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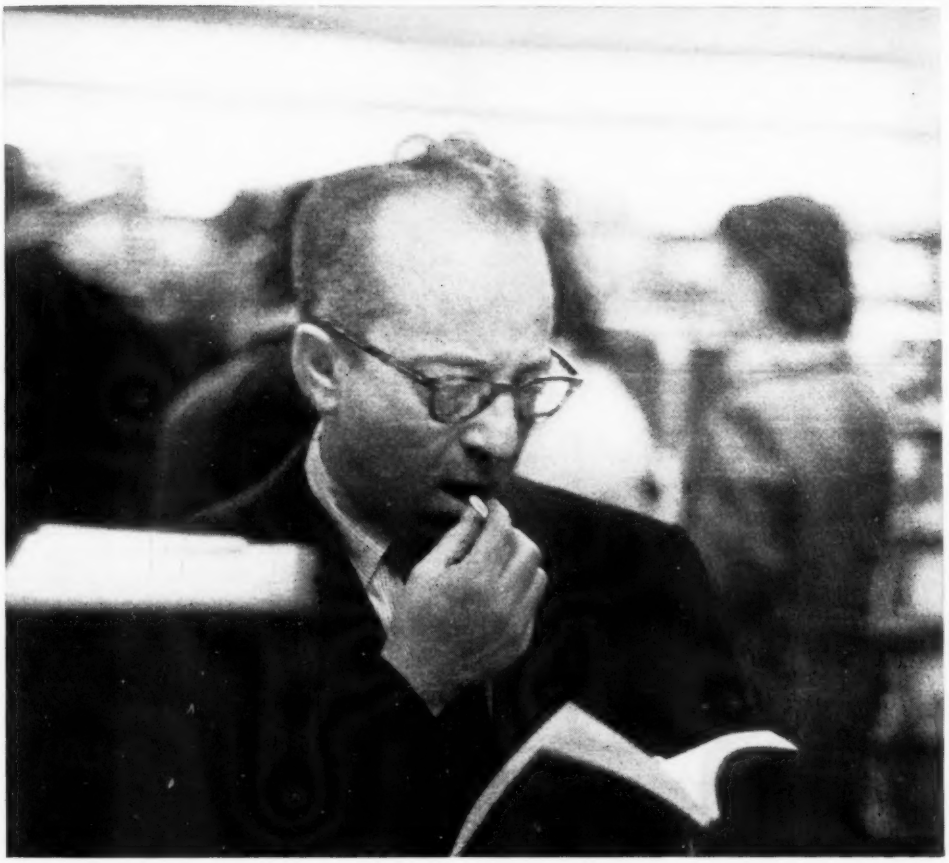

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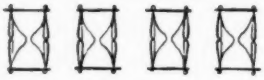
For the ambulant asthmatic: the only tablet that relieves asthma with nebulizer speed for 4 full hours 

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A Current Evaluation of the Antibiotics in Surgery

WILLIAM A. ALTEMEIER*

University of Cincinnati College of Medicine, Cincinnati

WILLIAM A. ALTEMEIER

THE current necessity of national preparedness for the care of mass casualties resulting from either enemy action or accidental explosion and the demands of everyday surgical practice have instigated this critical review. In my travels throughout the United States and other areas, I have been impressed with the growing feeling among many physicians that there is no longer any problem in the management of surgical infections, and that surgical infections are almost nonexistent. This, to me, indicates the blind reliance and false sense of security which many physicians have in regard to antibiotic therapy.

Antibiotic therapy may so mask infections that they may be completely overlooked unless careful searches for them are made. I recall making rounds in one hospital where there were 31 patients with penetrating wounds of the abdomen. I was told that there was no problem in managing these patients and that significant infection was not present. However, on examination I found that 29 of the 31 had serious infections, four of them massive subphrenic abscesses which, when drained, yielded from 500 to 2000 cc. of pus. These and other considerations have led me to this review of the existing knowledge of antibiotic agents and to a reconsideration of their relative position in everyday surgical practice.

There is no doubt that antibiotic therapy has had a profound effect on the practice of surgery. However, cumulative experience has proved that antibiotic therapy should be used primarily, in surgical practice, as a supportive or adjunctive measure to the indicated operative procedure. The evidence also indicates that the haphazard or careless use of the various antibiotic agents now available may actually produce harmful effects.

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Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

A knowledge of the effectiveness of the various antibiotic agents is imperative in order to obtain the best results in preventing and treating infections. There is no panacea, no single agent that can be used routinely or tolerated by every patient.

In civilian surgical practice, the prophylactic use of antibiotics has spread to the point where it is now completely out of hand. However, it can be of value, in my opinion, under the following conditions:

1. Elective surgical procedures performed in contaminated or infected areas, such as the gastrointestinal, respiratory or genitourinary tract.
2. Contaminated wounds of violence.
3. Cases in which an indwelling catheter becomes necessary as a supportive method of therapy.
4. Surgical procedures in patients who have derangement of the urinary tract.
5. Emergency operations in the presence of associated and unrelated infection, such as acute upper respiratory infection.
6. Injuries or operations of the oral and pharyngeal cavities in patients with pre-existing heart disease.
7. Probably, operations on elderly patients with pre-existing pulmonary disease.

In these instances one should choose the antibiotic agent on the basis of the anticipated or known bacterial flora and should administer it systemically and early. There is rarely any need for the topical application of antibiotics to contaminated wounds or cavities. The routine use of antibiotic agents after elective surgical procedures in clean operative fields, in my opinion, is not indicated and is responsible for some of the present hazards and pitfalls confronting us. A spot check of the patients at our hospital has indicated that the so-called routine use of antibiotic agents for elective surgical cases has decreased tremendously in the past year and that their use is now based on the conditions I have just described.

The use of antibacterial agents to prevent or suppress infections developing in contaminated wounds deserves special discussion. Their chief value lies in the attenuation, limitation or control of infection caused by residual bacteria in the wound after débridement, or the localization of infection developing within the wounds of patients for whom surgical treatment is necessarily delayed or impossible.

In both civilian and military practice, these agents have unquestionably produced significant results in controlling wound infections and reducing mortality. In the Korean war the over-all mortality for those men who survived their wounds immediately was 2.4 per cent. This low figure, I am sure, stemmed largely from the use of antibiotic agents as well as from the early operative treatment made possible through the rapid transportation of the wounded to the surgical centers.

On the other hand, infections complicating wounds of violence, in both military and civilian practice, still remain an important problem, antibiotic therapy notwithstanding. Although antibiotic therapy did not and does not prevent infection in many instances, it masks the infection or attenuates it.

A study has been made of the current practices which are limiting the wounded patient's response to antibacterial therapy. In general, the main reliance on antibiotic prophylaxis in patients with accidental or contaminated wounds, for some reason, has been shifted to the use of procaine penicillin in doses of 300,000 or 600,000 units. This is usually given with 500 mg. of streptomycin, the two agents being administered intramuscularly. I feel that this shift is ill-advised and unwarranted. The antibiotic levels in blood and tissue obtained with procaine penicillin are inadequate to control or suppress many of the fecal and soil bacteria which find their way into wounds. In addition, traumatized patients frequently are in shock which results in a very capricious and unsatisfactory absorption of antibiotics given intramuscularly. In fact, the absorption may be hindered or delayed to such an extent that an appreciable concentration of penicillin given intramuscularly may not be found in the area of the wound in some instances. The evidence suggests that patients who have undergone trauma and who have contaminated wounds should receive the aque-

ous type of penicillin G, not the procaine. If there is shock or impending shock, the penicillin should be administered intravenously and not intramuscularly.

When there is gross contamination by fecal bacteria, the use of aqueous penicillin intravenously should be augmented by the intravenous injection of 500 mg. of either chloramphenicol, tetracycline, chlortetracycline or oxytetracycline. This should be repeated at intervals of 8 to 12 hours for a period of 72 hours. After that period, the need for further use of these agents should be critically reevaluated.

In regard to the therapy of established surgical infections, clinical practice and experience have shown that the effectiveness of antibiotic therapy depends on certain factors, principles and premises, which, if observed, will frequently provide an excellent response. If we fail to observe them, the response will be haphazard or inadequate or may actually result in failure.

Generally speaking, infections respond best when they are in the diffuse or cellulitic stage, when the infected area still has an intact blood supply, and when the bacteria are growing at an extremely rapid rate. It is under such circumstances that the effect of the antibiotic agent is greatest and is usually followed by prompt regression of the infection and spontaneous resolution without abscess formation or necrosis of tissue.

On the other hand, when a late diagnosis is made and the infection has become well established, local necrosis, abscess formation or systemic invasion will have occurred. Even under these conditions, one can depend on antibiotic therapy to overcome the invasive qualities of the infection and to permit safer operative treatment, should that be necessary.

An example of such a situation is the case of a patient who had a burn on his arm that became infected with a hemolytic *Streptococcus*. The infection was four days old, invasion of the systemic blood stream had occurred, and he had a profound septicemia associated with septic shock. Treatment with penicillin controlled the invasive qualities of the infection, overcame the septicemia, and saved the patient's life, but did not prevent necrosis of tissues. After control of the infection, the necrotic area was excised and then grafted.

In seeing patients in consultation, I am frequently impressed with the fact that many physicians expect the impossible from antibiotics. In the case of an extremity that has no blood supply or an extremely limited blood supply, they frequently complain that the antibiotics have not brought the infection under control or permitted healing. When an extremity is cadaverous in appearance, obviously the surgeon has no right to expect antibiotic therapy to promote healing or prevent infection. Such a limb does not have an adequate blood supply for ordinary metabolic needs, let alone an adequate concentration of the antibiotics. Even if one applied the antibiotics locally, the blood supply would be inadequate to produce granulation tissue and healing.

A correct clinical diagnosis is more important now than ever. I find that the growing tendency of physicians to accept the laboratory reports on cultures has produced many false impressions and diagnoses and many failures of antibiotic therapy.

For example, one patient was treated for six months with a variety of antibiotic and chemotherapeutic agents, to no avail. The reason should have been apparent but was not. The treatment was based on the organisms that were cultured from the ulcerative area. This case, however, was an example of a burrowing anaerobic streptococcal infection. All the antibiotic therapy in the world would not produce healing of that lesion until incision of its entire extent or complete excision of the tract could be accomplished. Only then would the use of antibiotic therapy be followed by prompt healing and complete control of the infection.

In another case the patient had been treated for three months for "an unusual and undetermined infection." A variety of bacteria had been cultured from the lesion and the treatment based on the bacteria isolated. One look at the lesion or a similar one should have suggested a diagnosis of a self-induced or artifactitious lesion. The presence of gangrene,

without the associated cellulitis and without the manifestations of an infection capable of producing gangrene, should arouse suspicion that in all probability the wound is self-produced. Actually, that was the case in this particular instance.

Another patient had been treated for over a year with various forms of topical as well as systemic antibiotic therapy, again based on the results of surface cultures and not on a careful diagnosis resulting from biopsy or a hanging-drop smear. The correct diagnosis was blastomycosis, and healing occurred only after excision and skin graft.

A patient with a slowly progressing ulceration of the leg, associated with marked pain, had received antibiotic therapy for seven months based on the culture of the surface organisms. Treatment was completely ineffectual and the lesion continued to spread. Again the reason was obvious. The lesion in this case was an example of chronic progressive cutaneous gangrene that can be diagnosed only by its appearance and by the demonstration of the micro-aerophilic nonhemolytic *Streptococcus* in material aspirated from the zone of the advancing cellulitis. When the lesion was excised and antibiotic therapy used in conjunction with surgery, prompt healing and control of the infection resulted.

In this regard, I think that the trend at present is to try one antibiotic agent for three or four days; if benefit is not obtained, another one is tried, running through the list until one proves effective. Of course, this hit-and-miss system is apt to produce acquired resistance to bacteria and to mask the existing infection so that it spreads or produces marked necrosis.

If a patient who has septicemia does not show marked and definite response within 72 hours, one of several factors obtains. Either the treatment is based on the wrong etiologic agent, an obscure abscess or a secondary complication exists which has not been recognized, a superimposed infection has developed, or a vegetative endocarditis is present; the latter is particularly significant in patients with streptococcal and staphylococcal infections. It is important to remember that the vegetation may occur on either the right or the left side of the heart. On the right side it may be completely quiescent. For some reason not known to me, a vegetation on the tricuspid valve can give no symptoms or signs other than those of continuing sepsis. In the past two years I have seen in consultation seven patients with continuing uncontrolled septicemia in whom a silent endocarditis on the tricuspid valve was found at autopsy.

The actual selection of the antibiotic agent, of course, is of paramount importance. In some infections, particularly when the patient is desperately ill, it may be necessary to guess at the infecting agent. For example, in acute hematogenic osteomyelitis and septicemia the diagnosis has to be made on the basis of clinical evidence since x-rays will not give diagnostic information for five, seven or more days. During the early part of this infection the diagnosis can be made clinically, and treatment should be started promptly to obtain the best possible result with spontaneous and complete resolution of the process. Since over 99 per cent of the cases of acute osteomyelitis are caused by gram-positive organisms, in particular the hemolytic *Staphylococcus aureus*, penicillin would be the antibiotic of choice.

On the other hand, the haphazard use or selection of antibiotics on the basis of cultures alone may be quite misleading. For example, we found that the percentage of strains of hemolytic *Staph. aureus* which are susceptible to penicillin fell from 96 per cent in 1942 to 41 per cent in 1952. Since then, for some curious reason which is not apparent, the percentage of susceptible strains has increased. A little less than a year ago it was 57 per cent and at present it is 61 per cent. I was interested to note that at one of the Surgical Forums in Chicago another group of investigators reported a similar upswing.

It is interesting also that other bacteria have demonstrated the same fall in antibiotic sensitivity. The streptococci have usually remained quite sensitive to penicillin; many of the gram-negative organisms have become more or less resistant to various antibiotic agents, depending on the strain. Of particular importance to us has been the fact that

CHLOROMYCETIN® has maintained currently its antibacterial effectiveness against *Escherichia coli* and many of the other gram-negative organisms. At present, approximately 80 per cent of the gram-negative organisms isolated in our laboratory are sensitive to Chloromycetin.

Another trend is to treat lesions of the intestine with one antibiotic after another when surgery is clearly indicated. In one case of regional enteritis, by the time the patient finally came to operation all of the organisms of her intestinal tract were resistant to every antibiotic agent available. Hence she was subjected to the unwarranted increased hazard of infection with her surgery. A wound infection developed which we finally were able to control with the use of sulfadiazine.

Polymyxin B is by far the agent of choice in the treatment of *Bacillus pyocyaneus* infections. We have yet to find by in vitro tests a strain of this organism that is resistant to polymyxin B.

The timing of surgical intervention in patients with surgical infections is of the utmost importance. In many instances, emergency radical decompression is necessary within an hour or two after the onset of therapy; in others it is possible to delay surgical intervention for a day or two until the patient's condition can be improved. It is never excusable, in my mind, to treat a patient with antibiotics for weeks or months in an effort to forego surgical treatment which could cure him in a week or 10 days.

Supportive therapy is another aspect of treatment that frequently has been overlooked. In a case of far-advanced actinomycosis of the thorax, penicillin was ineffective until we treated the patient with massive transfusions of plasma and blood and corrected the alterations in physiology that had emanated from the uncontrolled and chronic infection. She has remained well.

In conclusion, I would like to say that until a few months ago I thought it was possible to predict the future of antibiotic therapy. However, some of the trends that have developed recently have indicated that such a prediction would be difficult to make.

The American physician is learning how to use the antibiotic agents more wisely and to recognize the hazards of their use. If he can be weaned away from any blind reliance on the antibiotic agents and re-educated as to the possible continued existence of surgical infections in a masked or attenuated form, we will have achieved a great step forward.

Postgraduate Clinical NOTES

51. PSYCHIATRY

Psychiatry has been called the "science of sympathy." The psychiatrist's most valuable tool is his ability to observe the patient and ask himself the question, "In this sufferer's position, how would I feel and how would I want to be treated?" This ability or capacity for empathy certainly is not the exclusive property of the psychiatric specialist. Naturally, the psychiatrist in his training and his experience acquires particular skills, knowledge and information regarding human behavior. Thus, he can be of great use in special and complicated problems and his services should be utilized. However, as all of us as physicians in our humanity become more sensitive to the totality of our patients as human beings, we shall have fewer cases which are hopelessly complicated.

Maurice J. Barry, Jr., Psychiatric aspects of diseases of the eye, ear, nose and throat, *Proceedings of the Staff Meetings of the Mayo Clinic*, May 2, 1956, p. 288

Hypogonadism in Middle-aged and Elderly Men

J. E. KIRK*

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I HAVE limited this survey of hypogonadism in middle-aged and elderly men to those types in which the characteristic feature is evidence of decreased androgen activity. It therefore covers only such conditions which can be classified by the terms hypo-androgenism and hypoleydigism and excludes hypogonadism in which the main defect is located in the seminiferous tubules.

J. E. KIRK

Recent investigations have contributed much to our understanding of the biochemical changes responsible for the development of hypogonadism in men with advancing age, and I shall review these biochemical aspects briefly before discussing the clinical diagnosis.

Figure 1 illustrates the current concept of the production of sex hormones. The stimulation originates in the hypothalamus. From there, the impulses pass to the anterior pituitary and cause secretion of the two gonadotropic hormones and ACTH. The interstitial cells of the testes, the Leydig cells, are the target organ for the interstitial cell-stimulating hormone (ICSH), whereas the follicle-stimulating hormone (FSH) acts on the spermatogenic cells in the seminiferous tubules. The Leydig cells, under the influence of the ICSH, produce androgenic hormones, and recent evidence indicates that testosterone is the main androgen produced by the human testes. The follicle-stimulating hormone, besides being important for the production and maturation of spermatozoa, is believed to cause the Sertoli cells to secrete estrogen.

Note also in figure 1 that ACTH is important for the production of sex hormones in the male. The ACTH released from the pituitary gland acts on the cells in the reticular zone of

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Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

the adrenal cortex, causing secretion of androgenic steroids and estrogen. The main androgenic steroids isolated from the adrenal cortex are adrenosterone and androstenedione. These adrenal steroids have a much smaller masculinizing effect than the testosterone produced by the Leydig cells of the testes.

Thus a lesion which produces hypogonadism may be located in the hypothalamus, in the anterior pituitary or in the testes. Hypogonadism due to a defect in the testicles is classified as primary hypogonadism, the term secondary hypogonadism applying when the lesion is in the hypothalamus or pituitary gland (table 1).

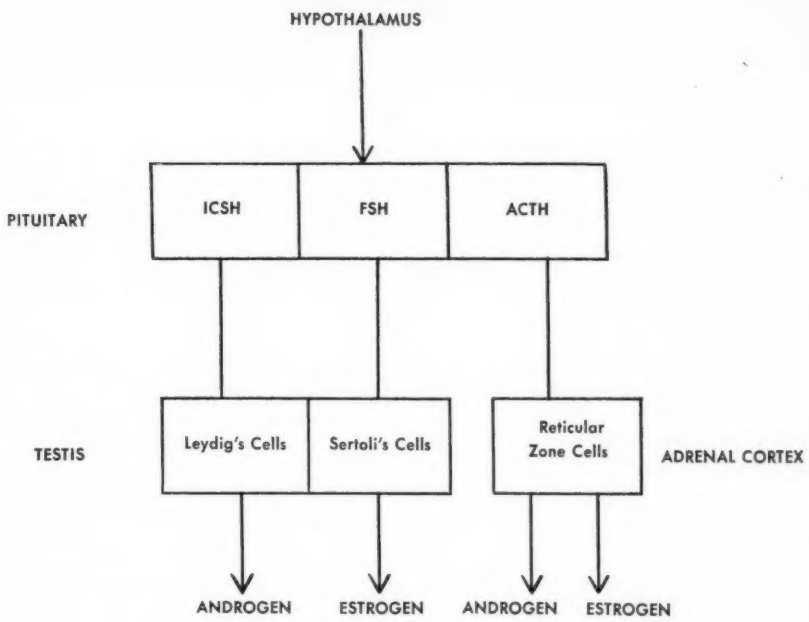

FIGURE 1. Current concept of production of sex hormones.

Pincus and associates[1] recently reported an extensive study on the effect of age on hormone production. They measured the urinary excretion of androgens, estrogens and corticosteroids in 297 men between the ages of 20 and 89 years. Table 2 summarizes the mean values observed. It is generally agreed that the urinary excretion of these hormones gives a fairly reliable measure of the rate of their production in the body. The androgen values shown in table 2 were obtained by the capon's comb method and therefore represent chiefly the testicular androgen, testosterone. These data demonstrate the important fact that testicular androgen production decreases markedly with advancing age in men, while in contrast the estrogen and corticosteroid production remains practically unchanged in men between the ages of 20 and 89 years.

There is a simpler method for determining androgen production than the capon's comb method, namely, by determining the urinary excretion of the neutral 17-ketosteroids.[2] These represent the metabolic end products of both the testicular and the adrenal androgens, about one-third being derived from the testes and two-thirds from the adrenals. Table 3 lists the mean 17-ketosteroid values found by Pincus and associates. Note that these values likewise show a marked decline with age. The results reported by Pincus et al. in 1954 agree with those reported by me in 1949.[3]

It is believed that the decreased production of androgen, particularly of the testicular androgen, testosterone, is directly responsible for the majority of the symptoms associated with functional hypogonadism. To explain the clinical symptoms more completely, however,

TABLE 1

CLASSIFICATION OF TYPES OF HYPOGONADISM

Primary	Testicular defect
Secondary	Pituitary defect Lesion of hypothalamus

TABLE 2

MEAN DAILY URINARY EXCRETION OF ANDROGENS, ESTROGENS AND CORTICOSTEROIDS IN 297 MEN BETWEEN THE AGES OF 20 AND 89 YEARS*

AGE GROUP (YEARS)	ANDROGENS (MG. ANDROSTERONE EQUIVALENT)	ESTROGENS (RAT UNITS)	CORTICOSTEROIDS (MG.)
20-29	3.7	11.5	2.19
30-39	2.8	12.4	2.02
40-49	1.5	12.0	2.57
50-59	1.4	10.6	2.23
60-69	1.4	9.6	2.13
70-79	1.6	12.5	1.87
80-89	0.5	10.5	1.93

*From Pincus and associates.[1]

we should consider also the two other groups of steroids, estrogens and corticosteroids.

As shown in table 2, production of both estrogens and corticosteroids remains practically unchanged in men with advancing age. Since androgen production declines markedly, the androgen-estrogen ratio and the androgen-corticosteroid ratio likewise will decline with age; the former decreases from 13.5 to 2.1 between the ages of 20 and 89 years, and the latter from 70.6 to 11.3 (table 4).

The decreasing androgen-estrogen ratio leads to increased estrogen stimulation of those tissues in the male organism which are sensitive to such stimulation—or, in other words, it leads to a certain degree of feminization. The prostate and the breasts have received special attention in this regard. Many investigators believe that the increased estrogen stimulation of the prostate contributes to the development of prostatic hypertrophy, whereas the effect of estrogen on the breasts is thought to be important in the development of gynecomastia in elderly men.

The decreased androgen-corticosteroid ratio also has clinical importance, since these two substances have opposite effects on protein

TABLE 3

MEAN DAILY URINARY EXCRETION OF NEUTRAL 17-KETOSTEROIDS IN MEN OF VARIOUS AGES

AGE GROUP (YEARS)	NEUTRAL 17-KETOSTEROIDS (MG. PER 24 HOURS)	
	Pincus et al., 1954[1] (*N* = 297)	*Kirk, 1949*[3] (*N* = 77)
20-29	12.6	
30-39	11.0	
40-49	10.3	10.5
50-59	7.9	8.8
60-69	7.6	7.0
70-79	5.3	5.3
80-89	4.4	4.3

TABLE 4

ANDROGEN-ESTROGEN AND ANDROGEN-CORTICOSTEROID RATIOS FOR MEN OF VARIOUS AGE GROUPS*

AGE GROUP (YEARS)	ANDROGEN-ESTROGEN RATIO	ANDROGEN-CORTICOSTEROID RATIO
20-29	13.5	70.6
30-39	9.4	57.7
40-49	5.1	23.6
50-59	5.6	27.0
60-69	6.0	27.2
70-79	5.3	35.1
80-89	2.1	11.3

*Calculated from data by Pincus and associates.[1]

(Androgens expressed as milligrams androsterone equivalent per hour x 1000. Estrogens: total estrogens in rat units per 24 hours. Corticosteroids: milligrams per 24 hours.)

TABLE 5

MAIN COMPLAINTS OF ELDERLY MEN WITH HYPOGONADISM

Sexual impotence
Muscular fatigue
Tiredness, lack of energy
Inability to remember as well as previously; poor concentration power
Lack of aggressiveness; indecision
General irritability; feeling of depression
Sleepiness during day; insomnia at night
Vasomotor instability

metabolism—androgens favoring the synthesis and corticosteroids the breakdown of body proteins. The relative increase in corticosteroid activity with age, therefore, will result in an increased tendency to a breakdown of body tissue, and this is believed to be one of the causes for lessened muscle volume and strength so often seen in middle-aged and elderly men.

Diagnosis

Although the investigations on the steroid hormones have contributed much to our understanding of the biochemical basis for hypogonadism in middle-aged and elderly men, the practical problem of establishing the diagnosis is not too simple. Mainly this is because the clinical symptoms are unspecific; i.e., similar symptoms may be due to senile changes in organs outside the endocrine system or to overwork or psychologic conflicts.

Table 5 lists the combination of symptoms which should make one suspect the presence of hypogonadism. Frequently these patients also have vague pains and aches involving all parts of the body, particularly the joints, and have attacks of palpitations, dizziness and paresthesias, the latter usually having the character of numbness and tingling of the fingers.

Physical examination gives comparatively little assistance in diagnosing hypogonadism in this age group, because the secondary sex characters, once they are established, usually regress only moderately as the result of declining androgen stimulation. There is one sign, however, which occasionally is of value, namely, the presence of gynecomastia. When palpation of the breasts indicates that the enlargement is due to an increase in ductal tissue and periductal stroma, the finding of gynecomastia definitely suggests hypogonadism. As already mentioned, gynecomastia is believed to be caused by a decrease in the androgen-estrogen ratio, with resulting increased estrogen stimulation.

TABLE 6

LABORATORY TESTS OF PRACTICAL VALUE FOR THE DIAGNOSIS OF HYPO-ANDROGENISM IN MIDDLE-AGED AND ELDERLY MEN

1. Determination of the acid phosphatase concentration of the prostatic fluid
2. Determination of the 24 hour urinary excretion of neutral 17-ketosteroids
3. Determination of the 24 hour urinary excretion of follicle-stimulating hormone

TABLE 7

ANALYSIS OF LABORATORY TEST RESULTS IN HYPOGONADISM IN MIDDLE-AGED AND ELDERLY MEN

1. *Acid phosphatase concentration of prostatic fluid*
(Normal value: 8000 to 14,000 units per milliliter)
8000 to 14,000 units per milliliter rules out hypogonadism
0 to 4000 units per milliliter is an inconclusive finding; indicates either prostatic degeneration or hypogonadism
2. *Excretion of neutral 17-ketosteroids*
(Normal excretion about 12 to 15 mg. daily)
12 mg. or above rules out hypogonadism
Values below 6 mg. are strongly suggestive of hypogonadism
3. *FSH excretion*
(Normal excretion 6 to 52 mouse units daily)
Above 100 units indicates testicular hypogonadism
0 to 4 units indicates pituitary hypogonadism

Usually it is impossible to establish the diagnosis of hypogonadism on the basis of the history or physical examination, and in most cases one must take recourse to laboratory analyses. The three laboratory tests which are of practical value in these cases, in my opinion, are listed in table 6, and table 7 summarizes the information which one can obtain from these tests.

Acid phosphatase concentration of prostatic fluid—This test is simple to perform. The reason it can be used as a measure of androgenic activity is that the prostatic secretion of acid phosphatase is a true secondary sex character in the male (figure 2). Acid phosphatase usually appears in the prostatic fluid at about 10 years of age.[4] During adolescence its concentration increases markedly to reach a value of about 14,000 units per milliliter at the age of 17 years. This value is about 100,000 times higher than the concentration of the enzyme in the serum. The prostatic fluid of individuals with hypogonadism shows either no phosphatase activity or a very low value.

In my opinion this test has great importance in the diagnosis of hypogonadism in children and young adults.[5] Its application in cases of middle-aged and elderly men is limited in that the acid phosphatase determination, in order to constitute a measure of androgenic activity, requires the presence of relatively intact prostatic tissue capable of responding to androgen stimulation with the production of acid phosphatase. Because the prostate in middle-aged and elderly men frequently is the site of degenerative changes, only the finding of normal phosphatase values (between 8000 and 14,000 units per milliliter) has diagnostic importance. However, since the *exclusion* of hypogonadism is one of the main problems with which one is confronted in clinical practice, the finding of a normal value aids greatly by making it possible to rule out hypogonadism.

TABLE 8

PERCENTAGE DISTRIBUTION OF PROSTATIC ACID PHOSPHATASE VALUES IN 175 INSTITUTIONALIZED MIDDLE-AGED AND ELDERLY MEN

AGE GROUP (YEARS)	NORMAL VALUE (8000-14,000 UNITS PER ML.) *Per Cent*	LOW VALUE (0-4000 UNITS PER ML.) *Per Cent*
40-49	61	21
50-59	53	21
60-69	33	25
70-79	31	42
80-89	17	67
90-100	14	72

A fairly high percentage of middle-aged and old men have normal acid phosphatase values, as shown in table 8, which gives the results of phosphatase determinations in 175 institutionalized men between the ages of 40 and 100 years. In the 40 to 60 year age group more than half had phosphatase values between 8000 and 14,000 units per milliliter, and about one-third of the 60 to 80 year age group likewise had normal values.

Schaus and I[6] recently developed a phosphatase test which can be performed in about five minutes and therefore has the character of a bedside method. The prostatic secretion is obtained by gentle massage of the prostate. The fluid is collected on a watch glass and may be either used immediately for analysis or drawn into a capillary for storage. At refrig-

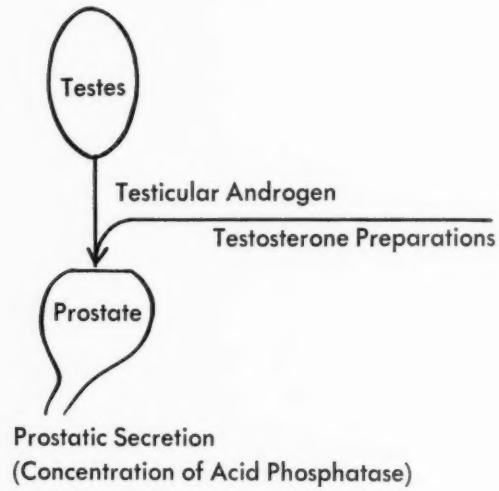

FIGURE 2. Androgenic activity as measured by the acid phosphatase concentration of prostatic fluid.

erator temperature the enzyme activity remains unchanged for at least one month. Measurement of the acid phosphatase activity is carried out by adding an aliquot portion of prostatic fluid by means of a micropipet to a solution of phenolphthalein phosphate in citric acid buffer (pH 4.9) and measuring the amount of phenolphthalein liberated from the substrate in three minutes at room temperature. The enzyme activity is stopped by adding a sodium carbonate solution. Development of a red color on addition of the alkali indicates the liberation of phenolphthalein, and its intensity is measured spectrophotometrically or by comparison with a set of permanent color standards.

Urinary excretion of 17-ketosteroids—If the phosphatase test shows a low value it will be necessary to take recourse to the other two tests listed in table 6. Determining the 17-ketosteroid excretion is a relatively simple colorimetric procedure, requiring only about two hours. The test in its ordinary form does not distinguish between the biologically active testicular androgen and the less active adrenal androgen but, as indicated in table 7, finding of values of 12 mg. or more will generally permit one to rule out the presence of hypogonadism, whereas a result below 6 mg. strongly suggests hypogonadism. Subjecting the ketosteroids to chromatography on an aluminum oxide column serves to make the analysis more specific;[7] the testicular ketosteroids will be found predominantly in area 3, where they can be assayed quantitatively. The chromatographic method is simpler than biologic assay by the capon's comb method, but it is too time-consuming for use in practice.

Urinary excretion of FSH—The third test also has considerable value, since a test result definitely above or below the normal range supports the diagnosis of hypogonadism. A high excretion of FSH (100 to 300 units or higher) is found in primary (testicular) hypogonadism and represents the pituitary's response to the reduced androgen level in the body. In contrast, the absence of FSH in the urine or the finding of very low values indicates involutionary changes in the pituitary gland (pituitary or secondary hypogonadism). The FSH test is rather expensive to perform, since it is based on biologic assay in mice. An objection has been raised in that it does not measure the hormone in which one is interested—namely, the ICSH. This objection, however, does not seem too important from a practical point of view, since the secretion of the two gonadotropic hormones, ICSH and FSH, runs parallel in most cases.

Of these three tests, only the FSH determination permits a distinction between testicular and pituitary hypogonadism. To be quite precise, however, I should point out that testicular degeneration may exist in connection with a pituitary involutionary lesion. Such coexistence of a testicular lesion will not reflect itself in the FSH analysis when the pituitary is the site of involutionary changes, since the pituitary gland will have lost its ability to respond to the low androgen level with increased production of FSH. For this reason, the actual differential diagnosis which one can make in elderly men with hypogonadism is between testicular deficiency and pituitary defect without or with coexisting testicular involution (table 9). Differentiating between primary and secondary hypogonadism is of little practical interest in middle-aged and old patients, however, since treatment in nearly all instances will consist of substitution therapy with testosterone regardless of the pathogenesis.

Treatment

The principles of substitution therapy with testosterone are so well established that a detailed discussion is unnecessary. I usually employ a dose of 10 to 25 mg. of testosterone propionate as an intramuscular injection two or three times weekly for four weeks. The dose is reduced to half this amount during the next

TABLE 9

DIFFERENTIAL DIAGNOSIS POSSIBLE THROUGH FSH ANALYSIS

Testicular degeneration
Pituitary defect without or with coexisting testicular involution

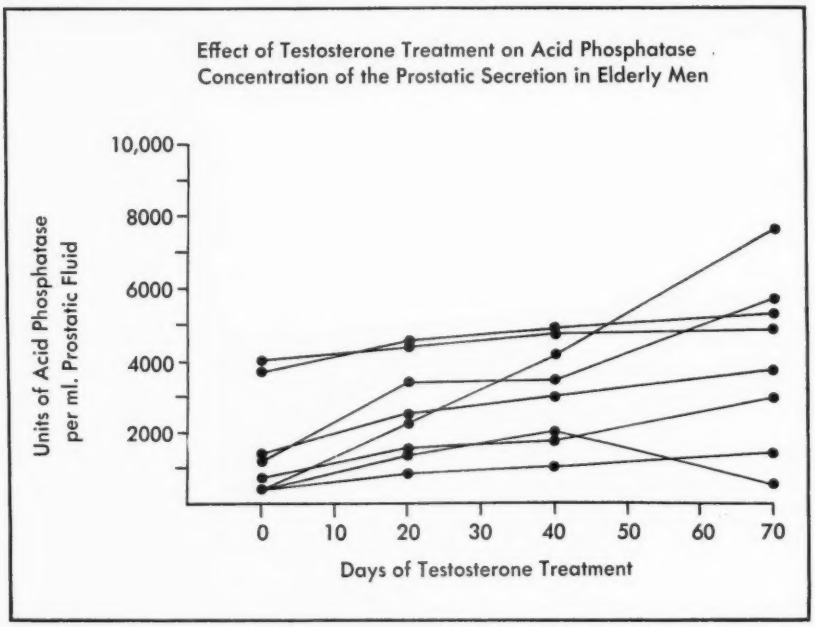

FIGURE 3.

month. Instead of testosterone propionate injections, one can give methyltestosterone, 10 to 15 mg. daily by mouth, with about equally good results.

Testosterone frequently affects the sexual impotence within a week, and it has been claimed that this quick response indicates that the effect is due to suggestion. I believe, however, on the basis of Wainman and Shipounoff's[8] studies on castrated rats, that it may be explained to some extent by an action of the hormone on the perineal muscles, the ischiocavernosus and bulbocavernosus, and that it is the improved tone and development of these muscles which make it possible for the patients to carry through an intercourse. The effect on the patient's tiredness, lack of energy and mental depression usually is noticeable within one or two weeks, and a large number of patients also have increased muscular strength and physical endurance after a few weeks.

One problem with regard to testosterone therapy of middle-aged and elderly men is the length of time one can continue treatment without producing undesirable changes in the seminiferous tubules. Several investigators have shown that administering 25 mg. of testosterone propionate three times weekly for three to six months may result in development of peritubular fibrosis in the testes. Although this fibrosis often regresses after cessation of testosterone therapy, it is recommended that to avoid this complication the dose be reduced to about 15 mg. testosterone propionate or 15 to 25 mg. methyltestosterone weekly whenever one wishes to continue treatment longer than two months.

The acid phosphatase concentration of the prostatic fluid increases in some cases during the course of testosterone therapy and remains low in others (figure 3). If a significant increase in phosphatase does not occur, one can conclude that the prostate is the site of degenerative changes.

I believe a therapeutic trial with testosterone is indicated also in instances where laboratory tests show borderline values. A two week treatment with placebos should be given first, followed by the usual dose of testosterone. The

effect of the administration of testosterone in the presence of hypogonadism usually is so evident that significant support for the diagnosis may be obtained in this way.

Summary

The current concept of the production of sex hormones in the male and of the biochemical changes responsible for development of hypo-androgenism in middle-aged and elderly men is reviewed. Clinical symptoms of hypogonadism in this age group are presented, with attention called to the fact that symptoms on the whole are unspecific since similar symptoms may be produced by senile changes in organs outside the endocrine system.

Secondary sex characters usually regress only moderately as the result of declining androgen stimulation, and therefore it usually is necessary to depend on laboratory measurements of androgenic activity for diagnosis of hypogonadism in this age group. The three tests which in my experience have proved of practical value are the determination of the acid phosphatase concentration of the prostatic fluid, the measurement of the 24 hour urinary excretion of neutral 17-ketosteroids, and the determination of the daily urinary excretion of follicle-stimulating hormone.

Differential diagnosis between primary (testicular) and secondary (pituitary) hypogonadism is of little practical importance in middle-aged and elderly men, since treatment consists of substitution therapy with testosterone preparations regardless of the pathogenesis of the condition.

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Postgraduate Clinical NOTES

52. HOBBIES

The strong recommendation of physicians to develop hobbies is not just a bright idea but is sound medical treatment based upon statistical evidence. Our studies showed that those persons who continued to work, even though they were past the usual age of retirement, were very likely to have many interests or hobbies. Also, the retired persons from our high socioeconomic group were very apt to occupy their time with planned activity. Both of these groups were relatively free of depressions and were quite different from those subjects requiring hospitalization because they were unable to adjust in the community. The people requiring hospitalization were almost devoid of any interests which could really satisfy their creative and recreational needs. For this reason, I believe the physician is responsible for making sure his patients who are approaching retirement or old age provide sources of entertainment and emotional rewards through planned creative and recreational activity.

E. W. Busse, Treatment of nonhospitalized emotionally disturbed, elderly persons, *Geriatrics*, April 1956, pp. 173-174

The Chronic Diarrheas: Classification and Diagnosis

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FROM the patient's point of view, chronic diarrhea is a major affliction; from the clinician's point of view, it is often a baffling problem. The reason lies in the multiplicity of causes of chronic diarrhea. The following analysis is made with a view toward simplifying the classification and the diagnostic approach to this troublesome condition. An attempt will be made to answer the questions: What do we mean by chronic diarrhea? How often does it present a diagnostic problem? How can this problem be solved without overlooking important pathologic conditions?

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Definition

Unfortunately, chronic diarrhea is not a disease entity or even a syndrome. It is simply a symptom no more specific than fever. Any definition of chronic diarrhea must obviously take into consideration the character of the stools as well as the frequency of passage. Chronic diarrhea can be defined as the intermittent or continuous occurrence of frequent loose bowel movements.

Incidence

Records of 4,431 consecutive patients who were admitted to Benjamin Franklin Clinic of Pennsylvania Hospital were reviewed before 200 cases of chronic diarrhea could be assembled. This number represents an incidence of 4.5 per cent among the patients examined in the clinic. It is extremely doubtful whether this incidence is applicable to the general population since most of the patients examined at

this clinic were referred because of unsolved diagnostic problems. Nevertheless, this figure should give one a general idea of how often this condition presents a significant problem in differential diagnosis.

Classification

To be of value to the clinician, any classification of the diarrheas should be brief and at the same time present the various types of diarrhea in some sort of logical order. Many classifications,[1] excellent from the point of view of completeness, have often lacked simplicity. Moreover, they have frequently failed to direct the clinician's thinking toward the nature of the disturbed function of the gastrointestinal tract. In an attempt to remedy this situation, I shall present a classification based on the primary functional disorder and accompanied by examples (table 1).

It should be clearly evident that a sharp differentiation between the various categories is not possible. In fact, when one considers that one is dealing with a single organ possessing several functions, it is not surprising or illogical to find that if a primary defect of one function exists there are associated disturbances in other functions. In each category I have attempted to include what I consider to be the primary abnormality or defect.

Diagnosis

Because of the number and wide variety of causes, a systemic approach to the problem of chronic diarrhea becomes essential. A careful history, a complete physical examination, certain routine and special laboratory tests, sigmoidoscopy, and roentgenographic study of the gastrointestinal tract are minimal requirements for establishing a diagnosis. Time and space permit discussion of only the salient features of each of these examinations.

History

1. *Age*—Defects of secretion and absorption may become apparent at any age. In early life, fibrocystic disease of the pancreas is encountered, while, later in life, sprue and, traditionally, diarrhea associated with achlorhydria are encountered.

TABLE 1

CLASSIFICATION OF CHRONIC DIARRHEAS

DEFECTS IN SECRETION
1. Hyposecretion
   a. Gastric
      (1) Atrophic gastritis
      (2) Postgastrectomy
   b. Pancreatic
      (1) Cystic fibrosis
      (2) Chronic pancreatitis
      (3) Neoplasms
2. Hypersecretion
   a. Small intestine
      (1) Sprue
   b. Large intestine
      (1) Irritable bowel

DEFECTS IN ABSORPTION
1. Hereditary constitutional defects
   a. Celiac disease
   b. Sprue
2. Acquired reduction of intestinal surface
   a. Resection
   b. Fistula

DISORDERS OF MOTILITY
1. Hypomotility
   a. Chronic constipation
2. Hypermotility
   a. Irritable bowel syndrome

INTESTINAL DISEASES
1. Bacterial infection
   a. Bacillary dysentery
2. Parasitic infestation
   a. Amebic dysentery
3. Nonspecific inflammation
   a. Regional enteritis
   b. Ulcerative colitis
4. Neoplastic infiltration
   a. Adenocarcinoma

INTESTINAL INJURIES
1. Chemical
   a. Mercurial drugs
   b. Laxatives
2. Physical
   a. Irradiation proctosigmoiditis

SYSTEMIC DISEASES
1. Endocrine
   a. Hyperthyroidism
   b. Diabetes
2. Allergic
   a. Gastrointestinal allergy
3. Other diseases
   a. Cirrhosis
   b. Nephrosis
   c. Leukemia

Disorders of motility increase in incidence with advancing age. Hypermotility associated with hypertonicity is by far the most common

disorder. The so-called irritable bowel syndrome is the outstanding example and is encountered with increasing frequency from age 20 onward. Oddly enough, hypomotility may be directly related to chronic recurring diarrhea. This condition is most often seen in elderly women who have been addicted to laxatives for years. In a number of these patients, atony develops. Recurring episodes of frequent, loose stools may be found to be associated with a large fecal impaction.

Intestinal diseases causing chronic diarrhea may be encountered at any age. Infants appear to be peculiarly susceptible to bacterial infection. Parasitic infestation can occur at any age, but in this country it is most commonly encountered during the age of greatest activity and travel. The nonspecific inflammatory diseases, regional enteritis and ulcerative colitis, usually appear in the second and third decades of life.

Intestinal injuries by drugs or irradiation may be expected to be seen in the older patient who is undergoing treatment for other conditions.

Systemic disease may occur at any age. Gastrointestinal allergy may appear early in life, while, in general, other systemic diseases may be expected later in life.

2. *Sex*—There is no correlation between sex and the causes of chronic diarrhea with the exception of celiac disease, which is more common in females, and carcinoma of the colon, which is twice as common in males. Irradiation proctosigmoiditis occurs almost exclusively in females who have received irradiation for pelvic cancer.

3. *Pain*—Pain is present in approximately one-half of the cases of defects of secretion and absorption. It consists of the lower abdominal crampy distress that is commonly seen in the irritable colon syndrome.

Defects of motility, characterized by hypomotility, are usually not accompanied by pain. In contrast, pain is a major symptom when hypermotility is associated with hypertonicity as seen in the irritable colon syndrome. The pain is characteristically crampy. It may migrate throughout the abdomen but is more commonly concentrated in the lower portions. It frequently comes on shortly after eating and is relieved by a bowel movement or the passage of flatus. It is characteristically made worse by the ingestion of irritating roughage and laxatives.

Intestinal diseases, bacterial in origin, do not cause a characteristic type of pain. When present, the distress is crampy in nature, wide in abdominal distribution, and frequently is precipitated by the ingestion of food and drink. Pain associated with various helminths may at times be quite severe and crampy. The hatching of the ova of *Strongyloides* in the small intestine is associated with a catarrhal inflammation and a persistent diarrhea.[2] Pain associated with amebic disease varies in intensity and is colonic in distribution. The pain accompanying nonspecific regional enteritis is mild unless the disease has progressed to an obstructive stage. In the latter instance, the pain will be distinctly peristaltic. In the majority of cases of nonspecific ulcerative colitis, the pain initially is mild but it later becomes colicky and precedes a loose, bloody bowel movement. In more than half of the cases of neoplastic lesions of the right portion of the colon, crampy pain is referred to the epigastrium. In the absence of obstruction, pain is not a prominent feature of neoplastic lesions of the left portion of the colon. When pain is present, it may be colicky and initially may be relieved by a bowel movement. As the disease progresses, a bowel movement may aggravate the distress.

Of the intestinal injuries, irradiation proctosigmoiditis may cause severe pain in the lower part of the back in addition to pain in the lower part of the abdomen and rectum.

4. *Tenesmus*—Tenesmus occurs during the acute phases of inflammatory diseases of the intestine. Rectal tenesmus accompanied by frank bleeding is a common symptom of carcinoma of the rectum and sigmoid.

5. *Time of bowel movements*—Defects of motility, notably the irritable bowel syndrome, cause diarrhea which occurs mostly in the forenoon as well as directly after eating. Rarely are patients awakened during the night because of diarrhea that is purely functional in origin.

Intestinal diseases of bacterial, parasitic or inflammatory origin may be associated with loose bowel movements at any time of the day or night. In some instances, the patient's rest may be seriously disturbed by the activity of the bowel.

Of the systemic diseases, allergy presents a peculiar problem because the diarrhea may appear shortly after the ingestion of a specific food or hours later. It has been suggested that the delayed reaction is caused by protein-split products of digestion and time is required for such digestion to take place.

6. *Inciting causes*—In defects of secretion as well as absorption, significant intolerance to particular types of foodstuffs such as animal fats or excess starch may be noted. In defects of motility, the symptoms are characteristically exaggerated in response to stress of any kind, whether it be dietary, emotional, infectious or endocrine. Chronic diarrhea was found to be closely related to emotional stress in more than half of the patients studied for this condition at the Benjamin Franklin Clinic.

In diseases of the intestine of bacterial or parasitic origin, a history of personal contact or travel into an area where the diseases are endemic may provide an important clue as to the cause.

Physical Examination

1. *Nutrition*—Nutrition seldom is affected in cases in which there is a defect in secretion of gastric juice; on the other hand, nutrition may be very poor in cases of pancreatic insufficiency. Undernutrition is an outstanding feature in cases in which there is a defect of absorption. Nutrition is rather good in most cases in which there is a defect of motility. In an occasional case of long-standing chronic diarrhea, the patient may present the picture of chronic malnutrition. In many cases of this type, causes other than diarrhea are responsible for the poor nutritional state.

In diseases of the intestine caused by parasites and not complicated by inadequate food supply, nutrition may be normal. In cases in which the food supply is deficient, e.g., in war prisoners, the combination of inadequate diet plus chronic diarrhea may result in a severe degree of malnutrition. The nonspecific inflammatory diseases are frequently but not invariably associated with a poor nutritional state. This condition is particularly common in diseases involving the small intestine. Neoplasm of the bowel does not result in undernutrition until late in the course of the disease.

2. *Skin*—In cases in which a defect in secretion of gastric juice is associated with diarrhea, anemia sufficient to cause pallor of the skin is extremely rare. Defects of absorption frequently include poor assimilation of iron. Pallor in these conditions may be extreme. In cases in which defects of motility are not complicated by absorptive disturbances, the color of the skin is generally good.

The outstanding characteristics of the skin in cases in which hypermotility is due to emotional causes are exaggerated sweating of the palms and alternate blushing and blanching of the skin of the face and neck.

In cases in which diseases of the intestine are associated with chronic loss of blood due to parasites, inflammation or neoplasm, pallor may be marked. In chronic disease of the liver, such stigmata as spider nevi and icterus suggest the possibility that malnutrition and vitamin deficiency may be important factors in causing the diarrhea.

3. *Abdominal distention*—Abdominal distention caused by excess gas is a frequent finding in cases in which there is a defect of secretion and absorption, and it is particularly common in the malabsorption syndrome. It is frequently described by patients with defects of motility, but it rarely is of visible proportions. In most instances, the distention is due to aerophagia which is a manifestation of a disturbed emotional state.

Diseases of the intestine due to parasitic infestation frequently are accompanied by abdominal distention. In uncomplicated, nonspecific inflammatory disease, the reverse is true. In neoplastic disease, abdominal distention is encountered late and may be due to ascites or intestinal obstruction. It also may occur in such systemic diseases as cirrhosis, congestive heart-failure and nephrosis, which are associated with ascites. In acute allergic episodes, gaseous distention which is accom-

panied by diarrhea may be marked.

4. *Abdominal tenderness*—Abdominal tenderness is characteristically absent in cases of uncomplicated defects of secretion and absorption. In cases of defects of motility, as, for example, the irritable bowel syndrome, tenderness may be present over the course of the entire colon but is particularly characteristic over the sigmoid, which can be felt as a narrow cord. In many instances, tenderness is also elicited over the cecum. Palpation may be followed shortly by a gurgling sound and disappearance of the previously noted tenderness. These characteristics are almost pathognomonic of the irritable colon syndrome.

In bacterial diseases of the intestine, abdominal tenderness may be generalized, but it is frequently localized over the course of the colon. In certain cases of amebic disease, tenderness may be confined to the cecal area. In regional enteritis, tenderness and an accompanying mass may be found in the right lower quadrant of the abdomen. In ulcerative colitis, the tenderness may be surprisingly mild for the degree of the inflammatory reaction present. It may be noted over the course of the entire colon or confined to the left lower quadrant. In cases of neoplasms, secondary ulceration and inflammation may result in tenderness localized over the lesion itself. However, in my experience, local abdominal tenderness has not been a characteristic or helpful sign of intestinal neoplasm.

5. *Abdominal mass*—In cases of defects of secretion and absorption, an abnormal abdominal mass is not a common finding unless an advanced neoplasm of the stomach or pancreas is present. An enlarged liver may suggest the presence of hepatic disease with secondary malnutrition and malabsorption. In cases of defects of motility, especially if hypomotility is marked, palpation may disclose phantom tumors[3] which are due to the accumulation of impacted feces and around which diarrheal stools may pass. Repeated examination after thorough cleansing of the bowel by means of enemas will usually suffice to eliminate the phantom tumor. Occasionally, additional measures such as limitation of the diet to clear liquids may be necessary for two or three days. When hypermotility is present in association with hypertonicity, as in the irritable bowel syndrome, the sigmoid colon is usually palpable as a firm, smooth, narrow cord.

In diseases of the intestine due to bacterial infection, abdominal masses are unusual. In amebic colitis, the liver may be secondarily involved and palpable. In terminal ileitis, a firm mass is often palpable in the right lower quadrant and is a valuable sign. In uncomplicated ulcerative colitis, usually no more than a palpable sigmoid colon is noted. In cases of neoplasm, the ability to palpate an abdominal mass will depend on the size and site of the lesion and on the presence or absence of obstruction.

6. *Abdominal peristalsis*—In defects of secretion and absorption, varying degrees of peristaltic activity may be encountered with a tendency toward increased activity in the majority of cases.

In defects of motility as typified by the irritable bowel syndrome, periods of violent activity alternate with periods of quiescence. During the periods of intense activity, intestinal noises may be grossly audible and may be a source of keen embarrassment to the patient.

In diseases of the intestine, continuous hyperperistalsis suggests organic obstruction.

Laboratory Examinations

1. *Blood count*—In defects of secretion, more particularly in gastric achlorhydria, the red cell count and the value for the hemoglobin usually are within the normal range.[4] In 6 of 27 cases in which the presence of histamine achlorhydria was discovered at the Benjamin Franklin Clinic, the value for the hemoglobin was between 12 and 13 gm. per 100 cc. of blood; in one case it was 10.7 gm., and in the remaining 20 cases it was more than 13 gm. In six of nine cases of pernicious anemia, the value for the hemoglobin was less than 13 gm.

In defects of absorption, the impairment may involve the assimilation of iron and result in hypochromic anemia of significant proportions. Of unusual interest is sprue in

which anemia may be macrocytic in type.

In defects of motility unrelated to a primary defect in absorption, the blood count is characteristically normal.

In diseases of the intestine due to bacterial infection, there is frequently a leukocytosis without any significant anemia. On the other hand, parasitic diseases of the intestine commonly result in an anemia of varying proportions with or without an accompanying eosinophilia. In nonspecific enteritis, an anemia is present due to nutritional insufficiency rather than to blood loss. In ulcerative colitis, in which anemia also may be present, blood loss is an important factor. In neoplastic diseases of the bowel, anemia usually is present only as a late manifestation.

In intestinal injury due to irradiation, a mild to moderate anemia is not unusual.

Among the systemic diseases, gastrointestinal allergy is suggested by the presence of eosinophilia. In actual practice, a normal eosinophil count is the rule rather than the exception.

2. *Stools*—In defects of secretion of gastric juice stools are said to contain grossly visible quantities of raw, undigested foods. As stated before, 27 patients with histamine achlorhydria were observed at the Benjamin Franklin Clinic. Six complained of chronic diarrhea but examination of the stools revealed incomplete digestion of food in only two patients. On the other hand, when definite deficiency in pancreatic enzymes occurs, striated meat fibers, excess neutral fat, and poorly digested starch granules are usually noted. A gross abnormality in fat or protein digestion, when noted in a routine stool examination, warrants further study by means of quantitative determinations of fecal fat and nitrogen. To be of value the analysis must be carried out under standardized conditions with the patient adhering to a known weighed diet such as the Schmidt diet. Under normal conditions the fecal residue on the Schmidt diet contains up to 6 per cent fat and 8 per cent nitrogen. In steatorrhea due to pancreatic deficiency the fecal nitrogen excretion is characteristically in excess of the normal 3 gm. per 24 hours.

In defects of absorption as seen in nontropical sprue, the stools characteristically are bulky, greasy and foul, and contain large quantities of fatty acids as well as neutral fat, excess nitrogen and starch. Calcium soaps may be present in sufficient quantity to result in lowering of the serum calcium levels.

In defects of motility, the stools are usually loose, fragmented and accompanied by mucus, but may alternately be scanty, firm and narrow. Digestion of vegetable matter is characteristically incomplete while the digestion of protein and fat is rarely affected except in cases of extreme hypermotility.

In diseases of the intestine, chronic diarrhea due to bacterial infection rarely results in bloody stools. Pus cells may be found on microscopic examination. Stool cultures are indicated when the patient is suspected of harboring an intestinal pathogen. In amebic colitis, the stools are intermittently loose and accompanied by blood and mucus. The opportunity to examine freshly passed bloody mucus should not be missed as it is in this material that typical trophozoites are most likely to be seen. Particularly during periods when normal stools are being passed, a minimum of three consecutive stools including at least one following a saline purge should be examined by using a concentration technic for ova and parasites. The value of this examination will depend in large measure on the skill and training of the examiner.

Patients suffering from regional enteritis characteristically may pass three to four loose stools a day accompanied by some pus and mucus but no gross blood. In contrast, the stools of patients with ulcerative colitis are frequently watery, grossly bloody, and contain mucus and pus. Patients suffering from neoplastic conditions of the bowel may exhibit little or no change in the character of their stools. The frequent urge to move the bowels with the subsequent passage of only small amounts of bloodstained mucus is characteristic of lesions situated low in the colon. The persistence of a positive reaction for occult blood in stools that otherwise appear normal requires a most careful search for an undisclosed source of bleeding that may well prove to be a neoplasm.

Of the intestinal injuries that might cause chronic diarrhea, one should consider that which sometimes follows the prolonged and injudicious use of certain antibiotics. The symptoms of enterocolitis that are encountered are probably not due to direct action of the drug on the bowel but to secondary effects associated with a drastic change in the normal intestinal flora. Under these circumstances, culture of the stool may be of great value in revealing the causative organism.

3. *Gastric analysis*—Defects in the secretion of gastric acid can be determined by means of intubation and fractional analysis after appropriate stimulation, or by the method of tubeless gastric analysis. It has long been thought that chronic diarrhea is often associated in some way with a lack of hydrochloric acid in the gastric juice. There is considerable doubt as to the existence of a direct cause-and-effect relationship. A recent documented study[4] revealed that diarrhea was the primary symptom in only 13 of 64 cases of histamine achlorhydria. This figure indicates an incidence of chronic diarrhea of around 20 per cent in patients with histamine achlorhydria. While this incidence is probably considerably higher than that in the general population, it does not seem sufficiently high to conclude that achlorhydria is a major factor in the production of chronic diarrhea.

In diseases of absorption such as celiac disease, hypoacidity may be found but it is not the primary factor.

4. *Duodenal drainage*—In diseases of secretion, especially those associated with a deficiency in the secretion of pancreatic enzymes, duodenal drainage in conjunction with stimulation of the pancreas may be helpful. Unfortunately, such a combined study involves a special technic and is a tedious procedure for both patient and physician. Nevertheless, the study may be crucial in determining whether the primary defect responsible for the diarrhea lies in the pancreas or elsewhere. It is especially indicated when other studies such as stool examination and a glucose tolerance test point toward pancreatic insufficiency as a possible source of difficulty.

In intestinal diseases, particularly parasitic infestations involving the small intestine, e.g., those due to *Strongyloides*, the recovery of the parasite in the duodenal aspirate may be the sole means of establishing the diagnosis since the results of stool examinations are frequently negative for these organisms.[2]

5. *Blood chemistry*—In defects of secretion, that due to pancreatic insufficiency is accompanied by a high or diabetic type of glucose tolerance curve.

In defects of absorption, as exemplified by the sprue syndrome, the glucose tolerance curve is characteristically low or flat. In severe cases, the serum calcium and serum protein may be lowered and the prothrombin time prolonged.

Among the diseases of the intestine, those associated with severe inflammatory reactions and profuse exudation may be accompanied by profound changes in the concentration of electrolytes and protein in the serum.

Among the systemic diseases that might cause diarrhea is overactivity of the thyroid gland. The presence of this condition can be confirmed by determining the basal metabolic rate or the uptake of radioactive iodine.

Sigmoidoscopy

In disorders of motility characterized by hypermotility, sigmoidoscopic examination is of value in revealing the presence of recently ingested food in the rectum. Undigested food particles in an otherwise normal stool suggest rapid passage through the intestinal tract. Particularly noteworthy is the observation that many patients with the irritable colon syndrome will experience a reproduction of their typical abdominal distress during the examination.

In intestinal diseases involving the rectosigmoid, sigmoidoscopy is of the greatest value. The characteristic lesions of the dysenteries, ulcerative colitis and neoplasm can be directly visualized and in most instances easily identified. Biopsy will permit differentiation between benign and malignant growths. Cultures taken directly from a typical lesion facilitate the identification of pathogenic organisms.[5] Of particular value in the recovery of the trophozoites of *Endamoeba histolytica* is the examination of fresh material aspirated

directly from the mucosa with the aid of a long glass tube attached to a suction bulb.

Roentgenologic Examination

In defects of secretion of gastric juice characterized by achlorhydria or hypochlorhydria, careful roentgenologic examination of the stomach is indicated because of the frequency with which malignancy is associated with low acid levels.[6] In defects of pancreatic secretion, careful roentgenologic study may disclose signs of pancreatic tumor, cyst or calcification, and suggest that the primary defect lies in a deficiency of pancreatic enzymes.

Of the defects of absorption, perhaps the most striking example is sprue. In the majority of cases of this disease, the roentgenologic findings are characteristic and consist of dilatation of the jejunum, segmentation of the barium column, coarsening of the folds, with evidence of hypersecretion and hypermotility.[7]

In defects of motility, delayed or unusually rapid passage of barium through the intestinal tract can easily be determined. The majority of patients with this defect fall into the irritable colon group. In these the typical roentgenologic signs include an increase in the number and depth of the haustrations of the colon accompanied by localized areas of spasm. Narrowing and loss of haustra of the left portion of the colon are also seen as well as unusual feathering of the marginal outlines associated with abnormal mucus secretion.

In intestinal diseases, roentgenologic study is of the greatest value. In chronic amebic dysentery, ulcers and granulomatous changes beyond the reach of the sigmoidoscope can be identified. In the absence of a roentgen examination of the typical distortion of the mucosal pattern accompanied by segmental narrowing of the lumen which may involve single or multiple areas of the small bowel, the diagnosis of regional enteritis cannot be made.

The roentgenologic study in ulcerative colitis may sometimes be misleading. When the typical shortening, narrowing and smoothing of the mucosal pattern or feathering of the marginal outlines are present, there is no problem. Unfortunately, there are times when sigmoidoscopic examination will reveal unmistakable evidence of ulcerative colitis but the changes will not be sufficiently advanced to be reflected in the roentgenologic picture. Undue reliance must not be placed on a negative roentgenologic report. In the diagnosis of neoplasm above the sigmoidoscopic level, the roentgenologic study is crucial.

Among the systemic diseases, allergy should be mentioned. Cases of proved gastrointestinal allergy are not common. In such cases, there is no specific roentgenologic picture, although patterns of disordered motor function are frequently described.

Allergy Studies

Allergy studies are indicated in cases in which there appears to be no obvious cause for the diarrhea and/or in which there is a personal or family history of allergy. Skin testing with various foods is of value only in so far as it may identify a potentially allergic subject. Further testing with elimination diets coupled with detailed food diaries is required before a positive diagnosis of true gastrointestinal allergy can be made. Prompt and dramatic relief of abdominal pain and diarrhea by the hypodermic administration of a few minims of ADRENALIN® is strongly suggestive of an allergic factor.

Psychiatric Evaluation

Psychiatric evaluation by a trained consultant is seldom necessary for diagnosis. A history taken with care and understanding will reveal only too clearly sources of anxiety and tension that may play a part in most diarrheas of functional origin. An important corollary is that when no obvious emotional cause is uncovered every step should be taken to exclude the presence of organic disease.

Principles of Management

Successful treatment depends on ascertaining the primary cause and taking steps to eliminate it or at least to ameliorate its effects. The chronic diarrheas associated with defects of secretion are often benefited by the replacement or substitution of substances lacking for proper digestion. Those associated with defects of absorption may be helped by

restricting the diet to those substances that are shown to be most easily utilized. Those diarrheas associated with disorders of motility may be relieved by eliminating irritating roughage in the diet and replacing it with bland, bulk-producing preparations.

The judicious use of antispasmodics and mild sedation may be a very helpful adjunct. It is most important to recognize that in the purely functional disorders no regimen can be expected to be completely effective under all circumstances. The diarrheas associated with specific diseases require specific treatment.

Conclusions

The chronic diarrheas represent a small but important fraction of medical practice. Because of the multiplicity of causes, a systematic approach is essential to the proper handling of this condition. Although the majority of chronic diarrheas appear to be functional in origin, serious organic disease may be overlooked unless careful steps are taken to exclude this possibility.

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Postgraduate Clinical NOTES

53. ATTENUATION OF ALLERGY IN AGED

It seems to be generally true that in individuals who have had allergies from early life, symptoms lessen in severity with age or, at times, disappear entirely. This may occur without specific treatment or general allergic management. Loss of symptoms may come about because specific sensitivities tend to have limited duration and "wear out," so to speak, although it sometimes takes many years for this to happen. However, while sensitivity to some substances disappears, hypersensitiveness to others may become manifest. There is also the possibility that sensitivity may take a new form —that is, produce a new type of clinical reaction. A patient may cease having nasal allergy from a specific food but may find the same food now produces urticaria or gastrointestinal symptoms.

The reason for this apparent attenuation of the allergic state is not clear. It may come because of certain physiochemical changes in the cells incident to the aging process. A characteristic of the allergic response is its explosiveness, or vigorous action. Because of endogenous changes, the cells in the shock tissue of most aging persons lose the ability or do not have the vitality to support a vigorous immunochemical reaction. Yet the immunology of the allergic state—the fundamental physiochemical reactions which result in the clinical manifestations of allergy—is said to be the same in the geriatric patient as in the young, only the threshold may be altered.

Solomon Slepian and Jacob Reicher, Allergy in the geriatric patient, *Geriatrics*, August 1956, pp. 339-343

Management of the Nephrotic Syndrome

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THE nephrotic syndrome is a clinical entity that is characterized by massive proteinuria, hypoalbuminemia and hypercholesterolemia, with or without edema.

Occurrence

The nephrotic syndrome occurs from early childhood to old age, and may be associated with a variety of renal and other disorders. Among them are "idiopathic" nephrotic syndrome or "nephrosis," hemorrhagic glomerulonephritis, diabetes mellitus, lupus erythematosus, amyloidosis, bilateral renal vein thrombosis,[1-5] constrictive pericarditis,[3] syphilis[6] and sensitivity to mercury,[7-9] gold,[10] bismuth,[11] TRIDIONE®,[12,13] paramethadione,[14,15] poison oak[16] and bee sting.[17] A recurrent form of the nephrotic syndrome has also been described; urine, serum proteins and cholesterol are normal in the edema-free intervals.[18] In a general hospital in which there are many diabetic patients, diabetes mellitus is the commonest disease associated with the nephrotic syndrome. In children, however, the syndrome is usually "idiopathic" or associated with hemorrhagic glomerulonephritis.

Pathology

A variety of renal pathologic changes has been found in those patients with the nephrotic syndrome who died or were subjected to renal biopsy during life.[19-24] The underlying renal pathologic picture varies from patient to patient according to the presence or absence of hematuria, hypertension and azotemia and also the nature of the diverse renal and systemic disorders already listed. In most cases, one of the following renal morphologic lesions will be found: diabetic glomerulosclerosis, membranous or lobular glomerulonephritis, glomerular amyloidosis, and bilateral renal vein thrombosis. If the nephrotic syndrome appears during the course of hemorrhagic glomerulonephritis, the lesions of membranous or lobular glomerulonephritis may develop on

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a background of exudative, proliferative or necrotizing glomerular changes. Except in the instance of bilateral renal vein thrombosis, a diffuse, distinctive glomerular lesion usually is found.

The tubular changes associated with the nephrotic syndrome are characterized by two striking findings in the epithelium of the proximal convoluted tubules: (1) an abundance of lipid, partially doubly refractile and (2) hyaline or colloid droplets or granules. Lipid is found in glomerular endothelial as well as in epithelial cells. The glomerular and tubular lesions found in the nephrotic syndrome were beautifully illustrated and carefully described by Allen.[20,23]

Of fundamental importance in considering the pathology of the nephrotic syndrome is the question of which lesions may revert to normal, with consequent recovery from the nephrotic syndrome. It may well be that the milder forms of glomerular involvement in the absence of systemic disease are capable of regression to normal, while the more severe forms of glomerular involvement, with or without coexistent systemic disease, tend to progress, with eventual obliteration of the involved glomeruli by collagen.

Pathologic Physiology

Edema—Regardless of the diversity of the glomerular lesions, massive proteinuria consequent to increased glomerular capillary permeability to plasma proteins, particularly albumin, is the initial and fundamental process in a series of complex and poorly understood mechanisms that are responsible for the development of the edema of the nephrotic syndrome.[25] As a consequence of the proteinuria, decrease in the plasma protein level, especially of the albumin fraction, develops. There is a resultant reduction of the colloid osmotic pressure of the blood plasma. This lowered pressure is believed to be the essential cause of the edema, although other factors, including changes in glomerular filtration rate, excessive reabsorption and retention of sodium, chloride and water, increase in capillary permeability due to generalized disease of the small blood vessels, the action of antidiuretic substances and sodium-retaining corticoid (aldosterone),[26,27] increased intrarenal pressure due to renal interstitial edema or to ascites, and the autonomic nerve influences, undoubtedly also play varying roles in causing and modifying the extent of the edema.

It is difficult to accept the loss of protein in the urine as the sole cause of the hypoproteinemia since in many cases of the nephrotic syndrome observed from the onset, the hypoproteinemia develops almost simultaneously with the proteinuria, while others show return to normal values of the plasma proteins in spite of the continued massive proteinuria. Although deficient synthesis of plasma albumin has not been demonstrated, an increased rate of catabolism of plasma albumin has been suggested as an important additional mechanism in the development of hypoalbuminemia.[28] In spite of the fact that there is a close correlation between the presence of edema and hypoalbuminemia, there are exceptions; there may also be spontaneous and other forms of diuresis, with reduction and/or disappearance of the edema, without appreciable change in the levels of the plasma proteins.

Obviously, the pathogenesis of edema in the nephrotic syndrome is still obscure and its clarification must await further study.

Hypercholesterolemia—The cause of the elevated levels of cholesterol in the blood is not known. Hypercholesterolemia is rarely absent unless vomiting, diarrhea or undernutrition has existed for a long period. Thyroid function is normal in patients with the nephrotic syndrome.

Urine—The urine contains massive quantities of protein. In addition, a variable amount of lipid is found owing to the leakage of lipids through permeable glomerular capillaries and the desquamation of lipid-laden tubular epithelial cells. Such lipids—doubly refractile bodies appearing singly or in masses, or in casts or oval fat bodies—may be seen in the urinary sediment with the aid of a polarizing microscope.[29] After vigorous shaking of a tube of urine, a zone of white foam forms above the level of the urine and does not disappear rapidly. The combination of massive proteinuria and large numbers of doubly re-

fractile bodies in the urinary sediment is pathognomonic of the nephrotic syndrome, regardless of the nature of the underlying glomerular morphologic picture. Hematuria of varying severity may be found. More severe degrees of hematuria are associated with active inflammatory or necrotizing glomerulitis.

Renal function—Variations in renal function are usually the consequences of the glomerular pathologic changes. However, tests of renal function often yield normal results unless extensive glomerular hyalinization develops with resultant permanent impairment of renal function and uremia.

Blood pressure—The blood pressure is usually normal in the idiopathic form of the nephrotic syndrome. However, hypertension may be found in association with hemorrhagic glomerulonephritis or diabetes mellitus. In those cases in which there is extensive glomerular hyalinization with obliteration of the capillary loops, sustained hypertension may develop. Hypertensive retinal vascular changes and cardiac enlargement consequently appear. In rare instances, the syndrome of malignant hypertension may supervene during the course of the nephrotic syndrome.

Cardiovascular phenomena[30]—The relation between the nephrotic syndrome and cardiovascular disorders is variable. In some instances the nephrotic syndrome is primary, and secondary hypertension may develop. On the other hand, the nephrotic syndrome may develop secondarily during the course of hemorrhagic glomerulonephritis or systemic disorders associated with hypertension. In diffuse visceral diseases, such as amyloidosis and lupus erythematosus, the nephrotic syndrome and cardiac involvement may coexist. In diabetes mellitus, the manifestations of the nephrotic syndrome and of hypertensive and arteriosclerotic heart disease may appear in succession. The prolonged elevation of the serum cholesterol which occurs in the nephrotic syndrome in young persons is believed to be one of the factors responsible for the development of coronary arteriosclerosis in that age group in which arteriosclerosis is relatively rare.[31] I have observed myocardial infarction in young nephrotics. The nephrotic syndrome may coexist with or simulate congestive heart-failure, especially in elderly patients with or without diabetes mellitus.

Clinical Considerations

Diagnosis—The physician should always attempt to answer two questions pertaining to the diagnosis: (1) Does the patient have the nephrotic syndrome? and (2) what is the underlying renal or systemic disorder associated with the nephrotic syndrome? The diagnosis of the *overt* form of the nephrotic syndrome is usually a simple matter. When edema is the presenting complaint, unmistakable laboratory evidence of the nephrotic syndrome will be found. The urine examination will reveal massive proteinuria and white foam after shaking; the sediment seen through the polarizing microscope will show doubly refractile and oval fat bodies. Hypoalbuminemia and hypercholesterolemia will also be found.

In a few instances, edema is not the presenting complaint; in fact, the patient may never have had edema. The diagnosis of the nephrotic syndrome should be suspected when a routine urine examination reveals massive proteinuria and the characteristic urinary sediment. The *latent* form of the syndrome is diagnosed when hypoalbuminemia and hypercholesterolemia are found together with the characteristic urinary abnormalities, all in the absence of edema.

It is essential to establish, if possible, the coexistence of a clinical renal or systemic disorder in a patient with the nephrotic syndrome. Careful history, physical examination and appropriate laboratory tests will establish the coexistence of hemorrhagic glomerulonephritis, diabetes mellitus, lupus erythematosus, amyloidosis, bilateral renal vein thrombosis, constrictive pericarditis, syphilis and sensitivity to mercury, gold, bismuth, Tridione, paramethadione, poison oak and bee sting. The diagnosis of the "idiopathic" nephrotic syndrome, a disorder seen most commonly in children, is made by excluding the renal and systemic disorders named above.

Hematuria of varying severity may be found in the nephrotic syndrome. Although milder degrees of hematuria may occur during the

course of the "idiopathic" nephrotic syndrome, moderate or severe hematuria is seen in those cases associated with hemorrhagic glomerulonephritis and lupus erythematosus.

Hypertension and transient, continuous or progressive azotemia may occur during the course of all varieties. In elderly diabetics, and some others, the nephrotic syndrome may coexist with renal insufficiency, congestive heart-failure and various forms of coronary insufficiency—angina pectoris, coronary failure and myocardial infarction.

Renal biopsy may be undertaken to establish the nature of the morphologic picture.

Differential diagnosis—Severe congestive heart-failure with massive proteinuria, cardiac and other forms of cirrhosis of the liver, idiopathic hypoproteinemia,[32] severe nutritional edema, and myxedema may present problems in the differential diagnosis of the nephrotic syndrome. If the fundamental laboratory evidence of the syndrome is kept in mind—massive proteinuria, hypoalbuminemia and hypercholesterolemia—the differentiation of these disorders from the nephrotic syndrome is rarely difficult.

Prognosis—The prognosis depends on the underlying renal or systemic disorder and the possibility of the reversal of the renal lesion as a result of spontaneous healing or of therapy. In general, children do better than adults, because the latter usually have coexisting systemic diseases. Patients now live longer with the nephrotic syndrome because bacterial infections such as erysipelas, peritonitis, pneumonia and others, which formerly were common causes of death, may be adequately treated with chemotherapeutic agents or antibiotics.

In view of the variety of clinical disorders which may be associated with the nephrotic syndrome, it is of the utmost importance to recognize those cases which may be the consequences of constrictive pericarditis, syphilis, or sensitivity to Tridione, paramethadione, gold, mercury and bismuth. In these conditions the indicated treatment or withdrawal of the offending drug or heavy metal may result in recovery. It should be borne in mind that many patients with the nephrotic syndrome of unknown etiology and those with associated acute hemorrhagic glomerulonephritis may also recover.

Recovery, characterized by the disappearance of edema and proteinuria and the return to normal values of the plasma proteins and serum cholesterol, may occur in several varieties of the nephrotic syndrome. Although the disappearance of proteinuria may indicate recovery, the nephrotic syndrome may recur after a period ranging from months to years. It appears necessary, therefore, to follow a patient who no longer exhibits proteinuria for a fairly long period before it is possible to speak of complete and permanent recovery. In some patients, recovery may be evidenced first by the development of postural proteinuria, which may later disappear. However, the nephrotic syndrome may recur after postural proteinuria has been present.

The patients who do not recover may continue to have exacerbations and remissions of the edema. This finally diminishes gradually and then disappears coincident with a decrease in proteinuria, return to normal levels of the plasma proteins and serum cholesterol, and the development of impairment in renal function, hypertension and finally renal insufficiency. Occasionally, the nephrotic syndrome may persist throughout the development of hypertension, renal insufficiency and uremia. In diabetes mellitus, the nephrotic syndrome may coexist with renal insufficiency, congestive heart-failure and the various forms of coronary insufficiency—angina pectoris, coronary failure and myocardial infarction.

Of fundamental importance in prognosis is the fact that the outlook is generally poor in cases in which the nephrotic syndrome develops during the course of diabetes mellitus, chronic hemorrhagic glomerulonephritis, amyloidosis, lupus erythematosus, bilateral renal vein thrombosis and severe mercury poisoning. Furthermore, in the idiopathic variety, persistent hematuria, azotemia and hypertension are associated with a poor prognosis.

Treatment

In view of the variety of clinical disorders which may be associated with the nephrotic syndrome, it is essential to recognize those

cases which may be the consequences of constrictive pericarditis, syphilis, or sensitivity to Tridione, paramethadione, gold and bismuth because the appropriate treatment or withdrawal of the offending drug or heavy metal may result in recovery. Such cases are distinctly uncommon.

More common are the cases of the idiopathic variety and those associated with diabetes mellitus, hemorrhagic glomerulonephritis, lupus erythematosus, bilateral renal vein thrombosis and amyloidosis. Recovery may occur in some cases associated with acute hemorrhagic glomerulonephritis or of the idiopathic variety. I have not seen recovery in cases associated with diabetes mellitus, chronic hemorrhagic glomerulonephritis, bilateral renal vein thrombosis, amyloidosis, lupus erythematosus and severe mercury poisoning. In the recoverable cases of the nephrotic syndrome, it is questionable whether the course of the underlying kidney disease is fundamentally influenced by any method of therapy; in view of the tendency to spontaneous recovery, it is indeed difficult to evaluate the effect of any treatment.

In spite of the fact that specific treatment is not available at present, proper management is still of great importance.[33,34] As in any disorder whose etiology is unknown, the treatment of the nephrotic syndrome is essentially symptomatic. The management includes general measures such as bed rest, regulation of diet and fluid intake, and the handling of specific problems such as infections and edema.

Bed rest—Bed rest is indicated when the patient has massive edema and ascites or an infection. Sudden and dramatic diuresis may follow a period of bed rest of two or three weeks. Otherwise, the patient is permitted to be up and about, even though some edema may be present. If the patient is a child of school age, arrangements should be made for a home teacher so that he may continue with his school work during the period of moderate edema. Adults with minimal edema are permitted to carry on their usual activities.

If the nephrotic syndrome is associated with acute hemorrhagic glomerulonephritis, bed rest is clearly indicated as long as hypertension and heart-failure persist, and until the urinary abnormalities have become stabilized.[35]

Hospitalization may be desirable for the treatment of severe infections and massive edema and for the necessary studies to enable the physician to evaluate the status of the patient.

Diet and fluid intake—The sodium content of the diet should be kept low, at approximately 1.0 to 1.5 gm. Only foods that contain minimal amounts of sodium are permitted, and these should be prepared and served without salt, soda or baking powder. Further restriction of the sodium intake is usually undesirable. Moderate amounts of salt-free condiments may be used. Modification of the sodium intake may be necessary if renal insufficiency or congestive heart-failure coexists with the nephrotic syndrome. The protein intake should be adequate, and a sufficient number of calories may be provided in carbohydrate and fat to maintain optimal nutrition. In diabetic patients, carbohydrate restriction may be necessary. The diet should be supplemented by the daily administration of a potent multivitamin preparation.

The restriction of fluids is unnecessary. Most patients lose their desire for fluid after the sodium intake has been limited.

Infections—The prevention and prompt treatment of infections eliminate a major danger to the patient with the nephrotic syndrome. Viral infections may be accompanied or followed by exacerbation of edema. In rare instances, remission of the edema and even recovery may occur after a viral infection. However, it is wise to avoid, if possible, exposure to upper respiratory infections. Bacterial infections, such as erysipelas, peritonitis, pneumonia and others, may be fatal in a nephrotic patient unless adequate antibacterial therapy is instituted as soon as these conditions develop. Remission of the edema and sometimes recovery may occur following such infections. Although the value of continuous prophylactic antibiotic therapy has not been established, I recommend such use of antibiotics, especially in children.

Edema—In considering the treatment of edema, the physician should be aware of the

possibility of spontaneous diuresis, with or without relation to infections, that may occur particularly in the recoverable forms of the nephrotic syndrome. However, in the presence of severe and symptomatic ascites, abdominal paracentesis not only may result in considerable relief but sometimes may be followed by profuse diuresis. Mercurial diuretics occasionally are effective. Temporary diuresis may occur following the intravenous administration of salt-free albumin or dextran. Large doses of urea, if tolerated, may be helpful in controlling edema.

Cation exchange resin therapy may be effective in some patients in inducing diuresis and maintaining them free of detectable edema.[36] However, electrolyte depletions of severe degree and gastrointestinal complaints may develop during such therapy.[37]

Nitrogen mustard may be used in the more resistant cases. It is questionable whether the results justify such drastic therapy.[38]

Malarial therapy with *Plasmodium vivax* has been found to be effective in some patients not only in inducing diuresis but also in effecting recovery.[39-42]

At present, ACTH and cortisone are the agents of choice in the treatment of the edema of the nephrotic syndrome because of their effectiveness in inducing diuresis, especially in the idiopathic form of the disorder.[33, 34, 43, 44] In such cases, use of the steroids has been associated with certain changes in the pathologic physiologic manifestations that tend toward improvement, i.e., increases in serum albumin and decreases in proteinuria, hypercholesterolemia and excessive potassium excretion. However, it is not known whether the fundamental disease process is beneficially influenced or whether the final outcome of the disease is favorably affected by such therapy.

In systemic disorders such as diabetes mellitus and lupus erythematosus associated with the nephrotic syndrome, hormone therapy may induce diuresis, but dangerous complications may frequently preclude the continued use of such treatment. Also, the systemic disease itself may be worsened by such therapy.

Steroid therapy should not be used in the presence of active infection, chronic renal insufficiency, congestive heart-failure and severe hypertension.

Before undertaking the use of steroids, the physician not only should be aware of the complications of such therapy but also should institute measures to prevent them, if possible, and be ready to discontinue the hormones if the life of the patient is threatened. The masking of infections and the development of dangerous electrolyte derangements and of severe and sustained hypertension constitute the important hazards. Throughout the course of hormone treatment, suitable dosage of antibiotics and potassium should be given, and blood pressure, blood electrolyte and other indicated blood chemical examinations should be carried out frequently.

The present plan of therapy with the steroids consists of administering ACTH in doses of 25 mg. intramuscularly every six hours for 10 to 14 days, or cortisone in doses of 50 mg. by mouth every six hours for 10 to 14 days. In the idiopathic form of the nephrotic syndrome, diuresis is induced in about three-fourths of the trials. If the initial course has been unsatisfactory, a second course may be given after five to seven days. Occasionally, diuresis is brought on only following a second or even a third course. On the other hand, diuresis may be induced during or after each of a series of courses of steroid therapy.

Prolonged intermittent or continuous steroid treatment has been carried out in patients with the idiopathic form of the nephrotic syndrome because of the possibility that it might favorably influence the basic disease and for the management of resistant edema.[45, 46] Even if such therapy does not produce cure, significant prolongation of life may be accomplished. In those patients who do recover, it is difficult to differentiate the effects of the steroid therapy from the natural course of the disorder.

Emotional Aspects

Much has been written concerning the emotional aspects of chronic illness and their manifestations in the patient and his family as well as in the physician responsible for the patient's care. The nephrotic syndrome is a

chronic illness but there are special problems that pertain to this disorder which are unique and often produce anxiety in the patient and his family and worry in the physician.

To the patient and his family, *edema is the illness* that imposes certain restrictions and requires repeated hospitalization for tests and treatment. Edema-consciousness develops soon after the diagnosis of the nephrotic syndrome is made. The patient and his family quickly become aware of the relations among the fluctuations of edema, weight and urinary output. The exacerbations and remissions of edema represent worsening and improvement of the disorder, and such variations may be associated with waxing or waning of anxiety. If the patient becomes free of edema, it may be difficult to obtain his cooperation for the necessary studies to establish whether recovery, latency, minimal constant proteinuria or postural proteinuria has developed. The patient who has not recovered shares with his family the constant fear of recurrence of the edema.

Sodium restriction may create eating problems, especially in children. The sodium restriction may create anxieties in the parents because similar restrictions may have been recommended for members of their families because of serious hypertensive or cardiac disorders.

The need to prevent infections imposes on the patient the necessity of restricting his contacts and of careful scrutiny of those who see him. As a result, he and his family may become abnormally infection-conscious and every sniffle may represent impending disaster.

As for the physician, unless he is familiar with the vagaries of the nephrotic syndrome, he may be subjected to worry as a result of his own ignorance and also by the need to relieve the anxieties of the patient or his family imposed by the disorder and its therapy. It is therefore essential that the physician feel secure in his knowledge of the nephrotic syndrome. He should be prepared to tell the patient or his family what is and what is not known about the disorder, i.e., cause, duration, recovery, recurrences, final outcome, treatment, and so on, in order to avoid such anxiety as uncertainty may produce. Successful management of emotional disorders in the nephrotic syndrome is indeed complex, taxing the resourcefulness and understanding of the physician.

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Books Received

New books received are acknowledged each month. As space permits, books of principal interest to our readers will be reviewed more extensively. Reviews will be found in this issue starting on page A-130 and additional listings on pages 379, 435 and A-138.

Virus Diseases and the Cardiovascular System. By Ernest Lyon, M.D., Jerusalem. Foreword by Paul D. White, M.D. 215 pages. 1956, Grune & Stratton, Inc., New York and London. $5.75.

The Neurosurgical Alleviation of Parkinsonism. By Irving S. Cooper, M.D., Director, Department of Neurosurgery, St. Barnabas Hospital, New York City. 104 pages with 68 figures. 1956, Charles C Thomas, Springfield, Illinois. $8.50.

Laboratory Tests in Common Use. By Solomon Garb, M.D., Assistant Professor of Clinical Pharmacology, Cornell University Medical College, New York. 160 pages. 1956, Springer Publishing Company, Inc., New York. $2.00.

Tabulae Haematologicae. By Dr. Karl Rohr, Zürich, Switzerland. 16 chapters, illustrated. 1956, Georg Thieme Verlag, Stuttgart, Germany. Distributed in the United States and Canada by Intercontinental Medical Book Corporation, New York. $2.00.

Of Water, Salt and Life. 1956, Lakeside Laboratories, Inc., Milwaukee. 72 pages with 31 plates. $7.50.

A Modern Pilgrim's Progress for Diabetics. By Garfield G. Duncan, M.D., Clinical Professor of Medicine, Jefferson Medical College, Philadelphia. 222 pages, illustrated. 1956, W. B. Saunders Company, Philadelphia and London. $2.50.

The Lung as a Mirror of Systemic Disease. By Eli H. Rubin, M.D., Professor of Clinical Medicine, Albert Einstein College of Medicine of Yeshiva University, New York City. 288 pages, illustrated. 1956, Charles C Thomas, Springfield, Illinois. $12.50.

Praktische Gastroenterologie. By Dr. Ernst Hafter with contributions by Dr. H. W. Hotz and Dr. F. Deucher. 380 pages with 258 illustrations on 148 figures. 1956, Georg Thieme Verlag, Stuttgart, Germany. Distributed in the United States and Canada by Intercontinental Medical Book Corporation, New York. $11.50.

The Nonvenereal Diseases of the Genitals. By Fritz T. Callomon, M.D., Formerly, Dermatologist, General Hospital and County Hospital, Bromberg, Germany, and John F. Wilson, M.D., Assistant Professor, Dermatology and Syphilology, Jefferson Medical College, Philadelphia. 382 pages with 150 illustrations. 1956, Charles C Thomas, Springfield, Illinois. $12.50.

Cryptococcosis; Torulosis or European Blastomycosis. By M. L. Littman, M.D., Department of Microbiology, The Mount Sinai Hospital, New York, and Lorenz E. Zimmerman, M.D., Central Laboratory, Veterans Administration, Armed Forces Institute of Pathology, Washington, D.C. 205 pages with 82 illustrations. 1956, Grune & Stratton, Inc., New York and London. $8.50.

The Clinical Diagnosis of Histoplasmosis

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It is readily apparent that there are no easily differentiated clinical symptoms of histoplasmosis, which epidemiologic evidence indicates affects millions of people, or this infection would long ago have been recognized and identified. Reference to the two most closely comparable granulomatous diseases, tuberculosis and coccidioidomycosis, readily supports this difficulty in the differential diagnosis of the mild or primary type of the infection, which is the type encountered in by far the greatest percentage of cases. The frequency of clinical symptoms accompanying infection with *Coccidioides* has been studied by Smith and his associates[1] among army personnel stationed in the San Joaquin valley. Even among this population with its readily available medical care, it was found that in 76 per cent of the cases the infection was asymptomatic or of such a mild nature as to go unrecognized. No comparable study of primary infection in cases of histoplasmosis or tuberculosis has been reported.

One must then approach this problem by recognizing that no pathognomonic clinical signs can be expected. The primary infection appears to have a spectrum varying from asymptomatic through mild, moderate to severe infection. Cases of so-called secondary infection or relapses will be discussed separately. Under present circumstances, it is probable that almost all of the mild and a large proportion of the severe infections are not recognized. This probably accounts for the mortality rate of more than 50 per cent in reported cases of culturally proved histoplasmosis.[2-5]

Difficulties and uncertainties in assessing the frequency and importance of a disease such as histoplasmosis, in which the concepts are changing so rapidly, are perhaps best illustrated by a recent report in which I stressed the importance of chronic cavitary histoplasmosis in a tuberculosis sanatorium.[6] Although

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this disease once was thought to be very rare, and although only 15 cases have been reported in the literature, it has been found to be a problem of great importance in tuberculosis sanatoriums.[7-10] Indeed, in one sanatorium of about 550 beds, it was found that active histoplasmosis probably accounted for between 5 and 10 per cent of the patients.[6] Actually, in 2.4 per cent of the patients, the presence of the disease was proved by culture or by pathologic demonstration of the *Histoplasma capsulatum*, and, in an additional 4.8 per cent, it was proved by serologic tests. The latter group of patients were classified as probably having an active form of the disease.

In this one sanatorium alone, a three year study has disclosed 20 patients who had chronic cavitary histoplasmosis in addition to 90 patients in whom the serologic tests were positive and who were classified as probably having histoplasmosis. It is immediately evident that if this incidence of between 5 and 10 per cent should be representative of the incidence of the disease in sanatoriums in areas where sensitivity to skin tests is high, cavitary histoplasmosis would be of tremendous importance and perhaps would account for as many as 1200 cases of active disease in sanatoriums in the high sensitivity area alone. In classifying the disease, one is thus subject to many difficulties owing to ignorance of the true prevalence of the disease.

Several attempts have been made to classify histoplasmosis clinically. The earlier attempts were made by Kunstadter, Whitcomb and Milzer,[11] Christie,[12] and Beadenkopf and Loosli.[13] More recently, Schwartz[14] made a clinical differentiation of pulmonary histoplasmosis but

TABLE 1

CHARACTERISTICS OF CLINICAL TYPES OF PULMONARY HISTOPLASMOSIS

CLINICAL TYPE		SYMPTOMS	TEMPERATURE	CHEST ROENTGENOGRAMS	AGE
Asymptomatic		None	?	Lesions probably are present in at least one-third of cases	Any age
Mild		Malaise and fever	Up to 100° or 101°	Lesions are present in at least one-third of cases. Two-thirds of lesions are nodular, one-fourth are pneumonic and one-tenth involve lymph nodes	Any age
Moderately severe		Malaise, fever and cough	Up to 104° or 105°	Atypical pneumonia	Any age
Severe	Acute epidemic	Fever, malaise, chest pain and cough	Up to 106°	Disseminated pneumonitis in both lungs	Young adults, workmen and soldiers
	Acute progressive	Spiking temperature, hepatomegaly, splenomegaly and diarrhea	Up to 106°	May be negative	The disease is especially common in very young and very old persons with other diseases
	Chronic progressive (cavitary)	Cough, sputum, malaise and fever	Mild, up to 100° or 101°	Fibrosis; cavitation (usually apical); calcified lesions observed frequently	Mostly over 50 years

he did not discuss the disease as a whole. Early in 1955, Loosli[15] and Peterson and Christie[16] described the disease in general among adults and children, attempting to classify it clinically. In March 1955, Smith[17] presented a table classifying the disease but did not include a clinical description of the various types.

After 10 years of experience with histoplasmosis, I am convinced that certain clear-cut clinical pictures are emerging and that it is of great importance to clarify these in terms of frequency, diagnosis and prognosis. The clinical spectrum of the disease as it is presently emerging can perhaps best be illustrated by table 1. The different clinical types of the disease will be described in detail. The disease varies from the severe, progressive, often fatal type to the moderately severe, mild and asymptomatic types.

Severe Histoplasmosis

In cases of this type of the disease, the patients are very ill. Serologic tests are positive, and skin tests often are positive, although they may be negative in cases in which the patients are critically ill. This type of the disease is divided into three subgroups.

Chronic progressive type (reinfection or cavitary)—This type tends to occur among older persons. It is characterized by a prolonged course, and it often lasts for years. The symptoms include cough, sputum, which sometimes is bloody, and malaise and loss of weight. The disease usually terminates fatally, although it may progress slowly and be characterized by repeated attacks and relative intermissions. The lungs usually are the site of chronic progressive changes and cavitation. Examination

TABLE 1 *(Continued)*

CHARACTERISTICS OF CLINICAL TYPES OF PULMONARY HISTOPLASMOSIS

FREQUENCY	DURATION	RELAPSES	RESULTS OF LABORATORY TESTS			PROGNOSIS
			Skin Test	*Serologic Test*	*Culture*	
?	?	?	+	?	?	Good
Probably frequent	1 to 4 days	?	+	±	?	Good
Probably frequent	5 to 15 days	Common in acute phase; may occur later	+	+	Probably positive early	Good
Fairly frequent	Up to 8 months	May occur	+	+	Positive early	Good; almost never fatal
Unknown; diagnosis often made at autopsy	1 to 6 weeks	Usually fatal	±	+	+	Almost always fatal
Incidence may be as high as 10 per cent in tuberculosis sanatoriums	1 to 10 years	Usual	+	+	+	Poor; eventually fatal

of the sputum and cultures usually will disclose *H. capsulatum*. The disease resembles chronic tuberculosis in every way. As mentioned previously, preliminary studies have revealed that as many as 1200 cases of active histoplasmosis may be found in tuberculosis sanatoriums in an area of high histoplasmin sensitivity. It is obvious that further studies of the prevalence of this type of the disease are both desirable and necessary, since it is so readily confused with chronic pulmonary tuberculosis. This confusion is readily evident by reference to figures 1 to 6 inclusive, which show roentgenograms made in six cases of proved histoplasmosis. These six cases will be reported briefly.

Case 1—The patient was a 31 year old white man whose illness began in October 1953 with chills, fever, a productive cough and weakness. He had lost 22 pounds. Roentgenographic examination of the chest revealed pulmonary infiltrations, and he was sent to a tuberculosis sanatorium.

Examination of the sputum did not disclose any acid-fast bacilli on 19 occasions between November 1953 and January 1954. Tuberculin and histoplasmin tests were positive, but the blastomycin and coccidioidin tests were negative. On two occasions, a culture of the gastric contents was negative for acid-fast bacilli. On January 11, 1954, and on a number of subsequent occasions, examination of the sputum disclosed *H. capsulatum*. In January 1954 and subsequently, complement fixation tests for histoplasmosis were positive. Roentgenographic examination of the chest revealed bilateral apical infiltration and bilateral cavitation (figure 1). Observation for one year has not shown any significant change.

FIGURE 1 *(case 1)*. Bilateral cavities in the upper lobes.

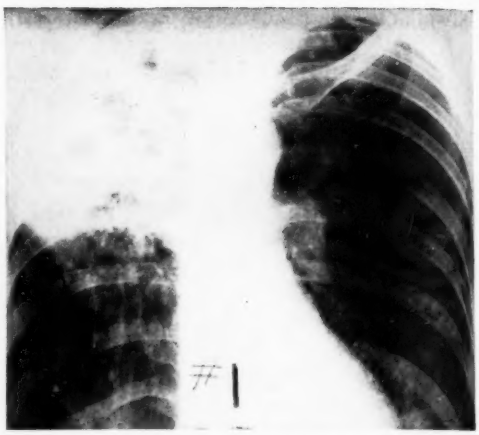

FIGURE 2 *(case 2)*. Multiple cavities and fibrosis of right upper lobe. Note hilar and peripheral calcification.

Case 2—A 58 year old white woman was admitted to a tuberculosis sanatorium in February 1953 because of a feeling of fatigue, loss of weight, and an increasing productive cough which had followed an attack of virus pneumonia which had occurred 13 months previously. She had been expectorating a considerable amount of sputum, which occasionally had been streaked with blood and often had been purulent. In January, her symptoms had increased. Nausea and vomiting had developed, and pain had occurred in the left upper quadrant of the abdomen.

Roentgenographic examination of the chest revealed pulmonary cavitation, infiltration in the right upper lobe and calcification in the hilar areas (figure 2). There also was evidence of old pleurisy at the base of the right lung. Microscopic examination of the sputum did not reveal any acid-fast bacilli on 19 occasions, and a culture was negative on two occasions. Examination of a bronchial smear also

FIGURE 3 *(case 3)*. Most of the left lung occupied by cavities. Small infiltration in right first interspace. Note calcified lesions in right lung.

did not disclose any acid-fast bacilli. A histoplasmin skin test was positive, but the tuberculin, blastomycin and coccidioidin tests were negative. On several occasions, examination of the sputum disclosed *H. capsulatum*. Complement fixation tests for histoplasmosis were positive.

Because of an increase of the pulmonary disease, the right lung was removed on September 25, 1953. Cultures of the excised lung were positive for *H. capsulatum*. The patient has improved steadily since the operation, and she gradually has gained 15 pounds. Roentgenographic examination of the chest has not shown any evidence of extension of the disease. Serologic tests for histoplasmosis continue to be positive.

Case 3—A 60 year old white man was admitted to a sanatorium in December 1953 because of massive hemoptysis. There was a three year history of weakness, easy fatigue, coughing and expectoration of sputum. Roentgenographic examination revealed infiltration at the site of the first intercostal space on the right side and cavities in the entire upper part of the left lung (figure 3). A large cystlike cavity occupied the apex.

A histoplasmin skin test was positive, but a tuberculin test was negative. Cultures for *H. capsulatum* were positive on at least two occasions. Serologic tests for histoplasmosis were positive.

The patient first was admitted to a hospital in January 1950. At that time, roentgenographic examination of the chest disclosed infiltration and cavitation. Since that time, similar examination has shown some progression in these changes. The patient has been under observation for a total of 54 months. Examination of smears of the sputum did not reveal any acid-fast bacilli on 12 occasions, and two cultures were negative.

Case 4—A 61 year old white man first was admitted to the hospital in February 1951 because of loss of weight, tiredness, and chest pain of 15 months' duration. In December 1950, x-ray examination disclosed bilateral pulmonary infiltration with cavitation and calcification in the left hilus (figure 4). Examination of the sputum did not reveal any acid-fast bacilli on 10 occasions, and three cultures were negative. Tuberculin and histoplasmin skin tests were positive, but the blastomycin and coccidioidin tests were negative. Examination of bronchial smears did not disclose any abnormality. Serologic tests for histoplasmosis were negative, but sputum cultures were positive for *H. capsulatum*.

FIGURE 4 *(case 4)*. Bilateral apical infiltration and cavitation. Note calcifications in left hilus.

After the patient had been in the hospital for two months, he left against the advice of his physician. He refused to return, but he recently consulted his physician because he was feeling ill and was losing weight and appetite. In 1954, roentgenographic examination revealed considerable extension of the disease in the left lung and some apparent contraction of the right lung. There still appeared to be cavities in the left lung. The results of recent serologic tests for histoplasmosis were doubtful.

Case 5—A 56 year old white man was first seen in December 1948, and was referred to a sanatorium because routine roentgenoscopy revealed pulmonary disease. He had had progressive dyspnea since 1945. At the time of his first admission to the hospital, roentgenographic examination revealed bilateral apical infiltration and calcification in several areas throughout the lung fields.

In 1953, his condition became considerably worse following the cutting of silage in an open field. His symptoms included chills, fever, weakness, loss of weight and a productive cough. Histoplasmin and tuberculin skin tests were positive, but the blastomycin and coccidioidin tests were negative. Examination of sputum smears did not disclose any acid-fast bacilli on 24 occasions, and seven cultures were negative. Complement fixation tests for histoplasmosis were strongly positive. In December 1953, *H. capsulatum* was isolated from the sputum. Cultures of the sputum were positive on four occasions. Roentgenographic examination revealed bilateral apical infiltration and cavitation of the left upper lobe (figure 5).

On August 13, 1954, pneumonolysis was performed preparatory to lobectomy on the left side. However, lobectomy was not performed owing to the extensive disease that was found when pneumonolysis was performed. The patient was returned to the ward in poor condition. Three days later, he died of postoperative shock. Autopsy revealed chronic granulomatous pneumonitis and postoperative hemorrhagic enterocolitis. It did not reveal any evidence of tuberculosis.

Case 6—A 59 year old white man was admitted to the hospital in October 1953, because of chills and fever of approximately 10 days' duration. He had lost about 30 pounds. A tuberculin test was negative, but a histoplasmin test was positive. A complement fixation test for histoplasmosis also was positive.

Roentgenographic examination revealed marked infiltration and cavitation in the upper lobe of the right lung (figure 6). Cultures for *H. capsulatum* were positive in December 1953 and at least on three occasions in May 1954. Examination of sputum smears did not disclose any acid-fast bacilli, and cultures for these bacilli were negative. Observation for 11 months has not shown any significant change in the roentgenographic findings.

Although this type of the disease is chronic and progressive, dissemination usually does not occur except in the terminal stage. This type of the disease has been described in the literature.[2,3,7] It appears likely that many more instances of the disease would be found if search were made in tuberculosis sanatoriums and in homes for chronically ill persons. Since serologic tests and cultures are uniformly positive, the diagnosis is relatively simple once suspicion of the presence of the disease has been aroused. Histoplasmin skin tests usually are positive.

FIGURE 5 *(case 5)*. Marked infiltration and cavitation of the left upper lung field with questionable infiltration in right second interspace. Note calcified lesions in both lungs.

FIGURE 6 *(case 6)*. Infiltration extending from the right apex to the third rib with cavitation.

Acute progressive type—This type of the disease is characterized by a short course. It usually does not last more than six weeks, and it usually is fatal. Physical and roentgenographic examination frequently does not reveal any pulmonary involvement. The disease often occurs in very young and very old persons, and in persons who have some other disease such as carcinoma, leukemia or tuberculosis. It is characterized by fever and enlargement of the liver and spleen. Dissemination to all organs of the body occurs early in the course of the disease.

This type of the disease frequently is described in the literature. Christie and his associates[4] have emphasized the frequency of gastrointestinal involvement in cases in which the disease occurs in children. In such cases, the symptoms consist of diarrhea and emaciation accompanied by enlargement of the liver and spleen. In cases in which the patients are adults, the symptoms may be largely pulmonary, and may also consist of cough, dyspnea and malaise, accompanied by hepatosplenomegaly. In older persons, the first sign may be a localized ulcer of the mucous membrane of the mouth, throat or larynx.

The disease has the characteristics of an overwhelming septicemia with a rapidly downhill course. Cultures of the blood and bone marrow are uniformly positive unless the patient is critically ill. *H. capsulatum* frequently can be seen in smears of bone marrow. At necropsy, cultures of most of the organs will reveal this fungus, which also can be demonstrated in tissue sections.

Acute epidemic type—This type is not progressive. It usually is associated with severe illness and disseminated pneumonitis which can be seen in the pulmonary roentgenogram. Recovery is the rule. The symptoms include fever, prostration, malaise and occasional pain in the chest. The patients usually do not have symptoms referable to the lungs. The illness may last from one week to eight months, but is rarely fatal. The extent of pulmonary involvement, as revealed by roentgenographic examination, often comes as a surprise to the physician because of the absence of physical findings. Another characteristic of this type of the disease is that roentgenograms made during the second or third week of the illness frequently reveal more involvement than those made during the first week. With healing of the pulmonary lesions, miliary calcification usually develops.

This type of histoplasmosis characteristically occurs in epidemics associated with a point source,[18,19] and it often affects families. The infectious agent appears to be airborne, as was shown on two occasions by the isolation of *H. capsulatum* from the air at the point sources of epidemics.[20] The organism also has been isolated from the soil or debris at the point sources of 17 of 30 such epidemics.[21]

Epidemics of histoplasmosis occur among adults who have not been infected previously. Thus, they most frequently occur in areas in which histoplasmin sensitivity is low or among military personnel from such areas who are serving in areas of high histoplasmin sensitivity. The characteristic roentgenographic appearance during the acute stage and after healing is shown in figures 7 to 10 inclusive. The roentgenograms shown in these figures were made in two cases (cases 7 and 8) which were observed in two epidemics among military personnel.

Case 7—The patient was a 29 year old sol-

FIGURE 7 *(case 7)*. Diffuse miliary pneumonitis of both lung fields with bilateral perihilar infiltration, more marked on the right.

FIGURE 8 *(case 7)*. Healed miliary calcifications scattered throughout both lung fields. Same patient as shown in figure 7 four years later.

dier who had lived in New York or New Jersey for 24 years. He spent one year at Camp Crowder. While he was at this camp in 1943, he had an illness which was characterized by shortness of breath, fever and weakness, and he was hospitalized for three months. Roentgenographic examination of the chest revealed diffuse miliary infiltration throughout both lung fields (figure 7).

A chest roentgenogram which was made in 1952 revealed miliary calcification (figure 8). At that time, a serologic test for histoplasmosis was positive. Tuberculin and histoplasmin skin tests also were positive, but a blastomycin test was negative.

The patient does not have any residual pulmonary symptoms. He does not know the source of his infection, but he was closely associated with a number of other men who had a similar illness.[18,19]

Case 8—The patient was a 25 year old soldier who had spent 22 years of his life in Georgia. In March 1944, he had an illness which was characterized by pulmonary symptoms, headache, a temperature of 106° F., and a stuffy feeling in his chest. In April of that year, roentgenographic examination revealed disseminated pulmonary infiltration (figure 9). While the patient was in the hospital, the disseminated pneumonitis improved somewhat, but resolution did not occur. After he had been in the hospital for eight months, he was discharged from the service with a 100 per cent disability rating because of pulmonary symptoms, difficulty in breathing, and failure to improve under treatment.

In 1950, he still was receiving a 10 per cent disability pension. In March of that year, a chest roentgenogram revealed disseminated miliary calcification (figure 10). In 1951, tuberculin, blastomycin and coccidioidin skin tests were negative, but a histoplasmin skin test was positive. A complement fixation test for histoplasmosis was strongly positive. At present, the patient does not have any symptoms except frequent colds.

This patient acquired his infection in a cave at Camp Gruber, Oklahoma. Of 39 soldiers who were exposed in this cave, 32 became ill, and 27 were hospitalized. This epidemic has been reported previously.[18,19]

Moderately Severe Histoplasmosis

This type of the disease is accompanied by rather severe influenzalike symptoms, and usually lasts for 5 to 15 days. The onset is

typically rather sudden, with cough and mild chest pains. Fever is usually present, and the temperature may rise as high as 104° F. Chest pain usually persists for only a day or so. Lassitude and malaise are definite and may be present for some days after recovery. Relapses with a rise in temperature and a recurrence of symptoms are not unusual.

Examination of the nose and throat rarely discloses any abnormality. Physical examination of the chest does not reveal any significant findings, but pulmonary lesions usually are demonstrable roentgenographically. The sedimentation rate of the erythrocytes characteristically is elevated. Since patients who have this type of the disease usually do not expectorate any sputum, cultures are not made.

In my experience, histoplasmin skin tests and serologic tests for histoplasmosis usually are positive when the tests are first performed, which, as a rule, is in the late stage of the illness. Occasionally, the results of either or both of these tests are negative when the tests are performed early in the course of the disease. To provide accurate diagnosis, therefore, the use of paired sera, as in virus diagnosis, is recommended. The first serum should be collected during the acute stage of the illness; the second, three or four weeks later.

A diagnosis of atypical pneumonia is made in many cases of this type of histoplasmosis, and a rise in cold agglutinins occasionally is observed. During the past several summers, I have been impressed by the frequency with which a diagnosis of atypical pneumonia has been made in cases in which serologic tests later proved that the patients, who were children, had histoplasmosis. In these cases, the chest roentgenograms showed pulmonary infiltration at one or more sites, and the infiltration was similar to that observed in many other diseases. Initial histoplasmin skin tests were positive, and serologic tests were markedly positive. In performing the serologic tests, a decreasing titer was evident with the passage of time.

Four cases (cases 9, 10, 11 and 12), one from each of the leading hospitals in the city, were investigated epidemiologically. In each of these cases, it was found that the illness occurred 7 to 14 days after a visit to a farm area where the child had played in a chicken coop. Several other children who visited the farms simultaneously also were found to be infected. From the point source of infection in three of these four cases, *H. capsulatum* has been recovered by animal inoculation. The chest roentgenograms that were made in the

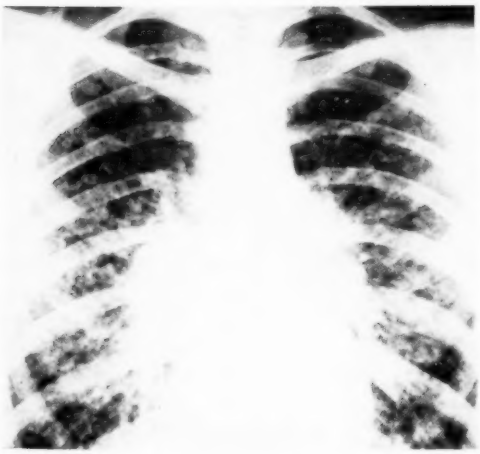

FIGURE 9 *(case 8)*. Disseminated pneumonitis of both lung fields. Note snowflake appearance and bilateral perihilar infiltration.

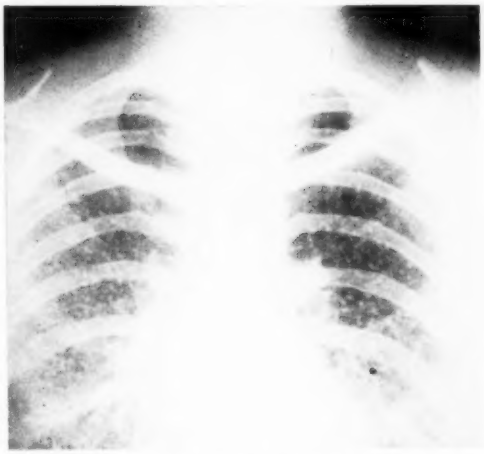

FIGURE 10 *(case 8)*. Same patient as shown in figure 9 showing development of miliary calcification six years later.

FIGURE 11 *(case 9)*. Pneumonic infiltration in first interspace on right with hilar and perihilar thickening.

four cases illustrate the nonspecific characteristics of the lesions (figures 11 to 14 inclusive). Figure 11 (case 9) shows a lesion which resembles tuberculosis with infiltration at the first intercostal space, figure 12 (case 10) shows enlargement of the lymph node at the right hilus, figure 13 (case 11) shows an infiltrate radiating from each hilar area, and figure 14 (case 12) shows rather poorly defined lesions throughout both lung fields and enlarged hilar shadows. These four cases will be reported briefly.

Case 9—A 12 year old girl first became ill with fever and malaise about July 15, 1953. The illness was not severe, and it lasted about one week. Because she had had severe pneumonia in 1947, chest roentgenograms had been made yearly until the end of 1951. During this time, the roentgenographic findings had been essentially normal.

On July 22, seven days after the onset of the illness, a chest roentgenogram revealed a minimal lesion of the pneumonic type at the site of the first intercostal space and enlargement of the lymph nodes at the right hilus (figure 11). The tuberculin skin test was negative and histoplasmin positive. Complement fixation and precipitin tests for histoplasmosis were positive three months after the onset of the illness, and they still were positive, but at a lower titer, 16 months later. At this time, a chest roentgenogram revealed that the lesion at the first interspace was still present but perhaps was a little *harder* than it was in the previous roentgenograms.

The child had visited the farm of an aunt for six weeks, and had returned home just before the onset of the illness. While she had been at the farm, she had collected eggs and had watered the chickens. A cousin who did not have any contact with the chickens did not become ill. Soil culture studies on the farm still are in progress.

Case 10—A seven year old boy was admitted to the hospital on August 17, 1953, because of intermittent fever, tiredness and poor appetite. A chest roentgenogram revealed perihilar infiltration (figure 12). A tuberculin skin test was negative, but a histoplasmin test was positive. The complement fixation and precipitin tests for histoplasmosis were positive.

The boy had spent three weeks (from July 19 to August 9) on his grandparents' farm. A number of cousins about his age were living on the farm. The boys had used an abandoned chicken brooder house as a clubhouse. On July 22, a rather extensive cleaning of the clubhouse was undertaken, and this raised a considerable amount of dust. An aunt and a cousin also became ill, but a serologic test did not reveal any evidence of active histoplasmosis.

Seven soil samples were collected from the farm of the grandparents. The only specimen that produced a positive culture for *H. capsulatum* was one from the brooder clubhouse.

Case 11—An 11 year old girl was admitted to the hospital on September 2, 1953, because of headache, fever and sore throat. She had become ill on August 25, and the initial symptoms had included headache and a sore throat. Later in the day, her temperature had been 100° F. She had continued to have a spiking temperature until she was admitted to the hospital. Her temperature had been as high as 104° F. She also had a hacking cough. She improved temporarily, but had a relapse.

A chest roentgenogram revealed infiltration at the base of the right lung and bilateral perihilar infiltration (figure 13). A histoplasmin skin test was positive, but the tuberculin,

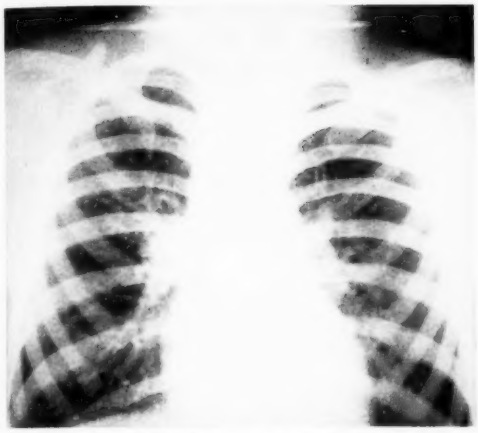

FIGURE 12 *(case 10)*. Hilar and perihilar infiltration on the right.

FIGURE 13 *(case 11)*. Bilateral hilar, perihilar and pneumonic infiltrations.

blastomycin and coccidioidin skin tests were negative. On September 9, a precipitin test for histoplasmosis was positive but a complement fixation test was negative; six weeks later, both of these tests were positive. Six months after the onset of the illness, the result of a precipitin test was classified as borderline positive, and the result of a complement fixation test was negative.

The child had visited her grandparents at their farm in Missouri from August 9 through August 22. On August 15 and 16, an aunt and two cousins from Iowa also had visited the farm. The three children had played in the chicken coop. About August 22, both of the cousins became ill with fever, cough and headache. One of the cousins was ill for several days; the other one, for four to six days. Follow-up studies of these children could not be obtained.

Six soil specimens were collected from the farm of the grandparents. The only specimens that produced a positive culture for *H. capsulatum* were one that was obtained from a chicken brooder house and one that was obtained from the chicken coop.

Case 12—A 13 year old boy was admitted to the hospital on September 14, 1953, because of fever, chest pain and malaise. He had become ill on August 22, and the initial symptoms had included chest pain and a temperature of 102° F. Physical examination had not disclosed any abnormality. The child had vomited once, and he had been confined to bed for 23 days before he was admitted to the hospital.

A chest roentgenogram revealed patchy density throughout both lungs (figure 14). The density was more marked in the hilar areas. Resolution has occurred slowly, and a chest roentgenogram made 11 months after the on-

FIGURE 14 *(case 12)*. Scattered patchy densities in both lung fields with right perihilar infiltration.

set of the illness revealed that the lungs were not entirely clear.

The complement fixation and precipitin tests for histoplasmosis were strongly positive when the patient was admitted to the hospital, and they were still positive 10 months later. The tuberculin, blastomycin and coccidioidin tests were negative, but a histoplasmin test was positive. The patient was hospitalized for nine days, and he improved slowly.

From August 15 to 18, 1953, the patient and his mother and sister had visited a farm owned by relatives. While the child was there, he had cleaned sparrows' nests out of an attic. On November 2, 1953, five soil samples were collected from about the farm. Samples obtained from the chicken house and near the foundation of the house in an area frequented by the chickens produced a positive culture for *H. capsulatum*.

In 1947, two of the patient's cousins had had a severe undiagnosed illness after they had cleaned out a room used to house chickens. Their symptoms had included vomiting, loss of weight and a temperature that had reached 104° F. Their illness had lasted three weeks. One of these children was followed. A histoplasmin skin test was positive, but a tuberculin test was negative. A serologic test for histoplasmosis likewise was negative. A chest roentgenogram revealed healed miliary calcification.

Since moderately severe histoplasmosis does not produce any characteristic clinical or roentgenographic findings, it is important that the physician should be aware of the possible presence of this disease and that he should use skin tests and serologic tests in an effort to make the correct diagnosis.

Mild Histoplasmosis

The frequency of this type of the disease among persons who become infected with *H. capsulatum* is not known. This type is characterized by mild, influenzalike symptoms which last for one to four days. Signs and symptoms of pulmonary involvement usually are not present.

Since roentgenographic examination reveals pulmonary infiltration in about one-third of the cases in which the result of a histoplasmin test on children is positive,[22] it is presumed that pulmonary infiltration occurs rather frequently. If this is true, one would expect that the infiltration would be of the nodular type (figure 15) in two-thirds of the cases. This type heals by calcification (figure 16). In about one-third of the cases, the infiltration would be of the pneumonic type (figures 17 and 18) and in a lesser number of cases it would involve only the lymph nodes (figures 19 and 20). Less than 1 per cent of the patients will have disseminated lesions which are characteristic of the epidemic type of the disease. This type will be considered later.

The following case reports serve to illustrate the findings in mild histoplasmosis. Roentgenograms of these cases are shown in figures 15 to 20.

Case 13—The patient was a nine year old boy. A roentgenogram which was made in the course of a routine school survey in 1946 disclosed nodular infiltration at the site of the second intercostal space on the left side and enlargement of the hilar lymph nodes (figure 15). Calcification was evident in the center of the infiltration. A tuberculin skin test was negative, but a histoplasmin test was positive. The sedimentation rate of the erythrocytes was 5 mm. in one hour. The patient had not

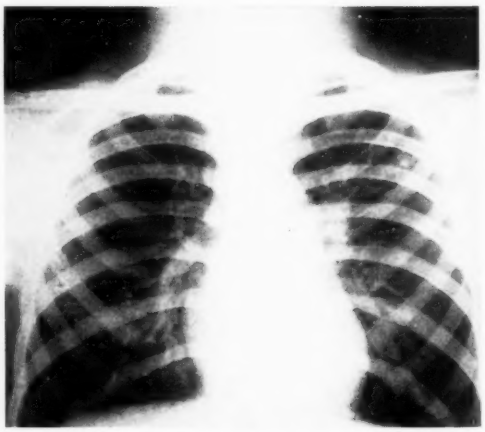

FIGURE 15 *(case 13)*. Nodular infiltrate with calcified center in left second interspace with enlarged hilar nodes.

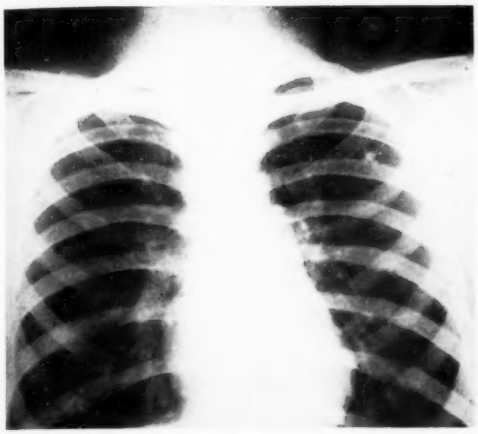

FIGURE 16 *(case 13)*. Development of calcification after five years. Note also calcification in hilar and mediastinal nodes.

had any previous illness except an attack of chorea which had occurred some time before the roentgenogram was made.

Complement fixation tests for histoplasmosis were not performed until March 1948. At that time, the result of the test was positive. The results of continued tests were strongly positive until October 1951. In March 1952, the result of the test was doubtful; in 1953, it was negative. Chest roentgenograms which were made during this interval revealed that the lesions were healing slowly. A roentgenogram which was made in 1951 revealed calcification of the lesion as well as the hilar and mediastinal lymph nodes (figure 16).

Case 14—The patient was a seven year old girl. A roentgenogram which was made in the course of a school survey in 1945 revealed definite infiltration in the lower part of the right lung. At that time, a tuberculin skin test was negative, but a histoplasmin test was positive. There was no history of a definite or unusual illness.

A complement fixation test for histoplasmosis was first performed in 1947, and the result of the test was classified as doubtfully positive. The next test was performed in 1954, and the result was negative.

Chest roentgenograms showed some hardening of the lesions as time passed. A roentgenogram which was made in 1947 revealed a clear-cut pneumonic area in the base of the right lung and a probable increase in the size of the hilar lymph nodes (figure 17). Subsequent roentgenograms showed evidence of gradual calcifications of the lesions. A roentgenogram which was made in 1954 revealed marked calcification (figure 18).

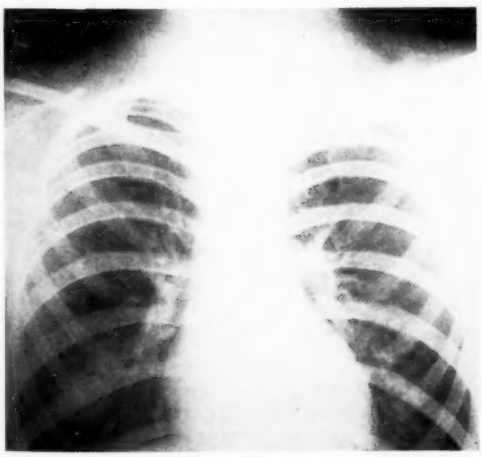

FIGURE 17 *(case 14)*. Pneumonic infiltrate in right lower lung field with hilar enlargement.

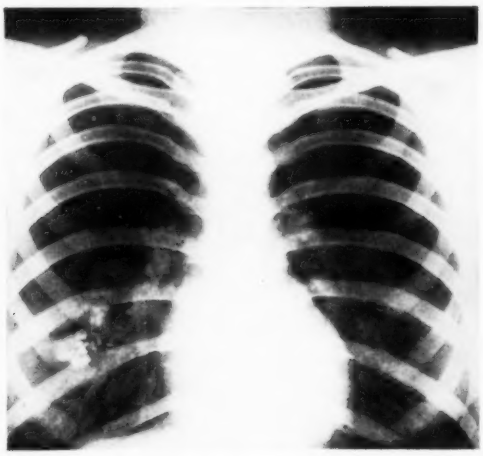

FIGURE 18 *(case 14)*. Development of calcification at site of earlier infiltrate seven years after date of figure 17.

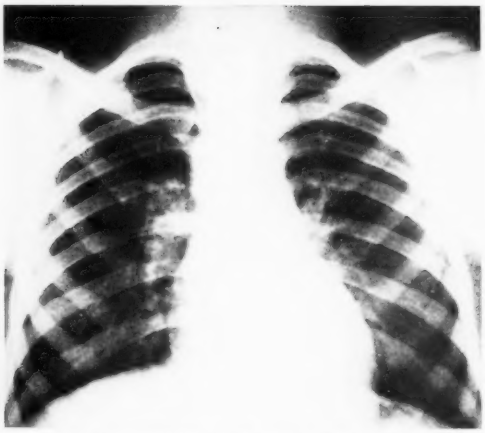

FIGURE 19 *(case 15)*. Markedly enlarged lymph nodes in right hilar area without evident parenchymal lesion.

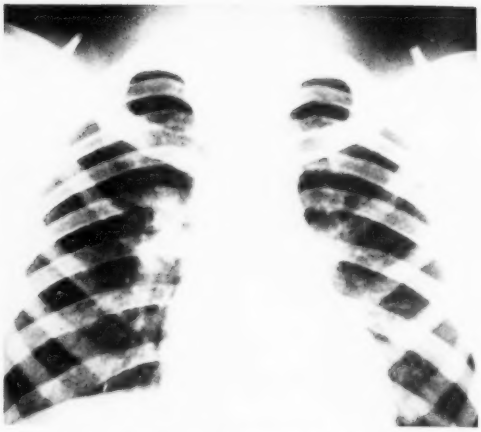

FIGURE 20 *(case 15)*. Calcification of the hilar lymph nodes four years after date of figure 19.

Case 15—The patient was a 10 year old Negro boy. A roentgenogram which was made in the course of a school survey in December 1945 revealed enlargement of the lymph nodes in the right hilus (figure 19). There was no history of a previous illness, and the boy was not ill when the roentgenogram was made. The histoplasmin skin test was positive and the tuberculin test was negative. Blastomycin and coccidioidin skin tests were performed subsequently and were found to be negative. Subsequent roentgenograms revealed that the lesion was healing gradually. The last roentgenogram was made in 1949, and it showed calcified deposits in the hilar area (figure 20).

Examination of laryngeal smears did not disclose *H. capsulatum*. The sedimentation rate of the erythrocytes was 16 mm. in one hour in 1946, and it remained elevated until 1949. The result of a complement fixation test for histoplasmosis was reported as doubtful in 1948, but in 1949 the test was strongly positive. The result of the test was doubtful in 1950 and negative in 1951.

In 4 of 22 cases in which the patients were infected while they were working with *H. capsulatum* in the laboratory, the disease was of the mild type. In each of the four cases, the influenzalike illness was severe enough to confine the patient to bed. When fever occurred it was mild. Malaise was a prominent symptom.

Asymptomatic Histoplasmosis

In the great majority of cases of histoplasmosis, the disease probably is of the asymptomatic type. The exact incidence of this type of the disease is unknown. It awaits further determination by studies such as those made by Smith and his associates[1] in cases of coccidioidomycosis. Such studies are now being made with the cooperation of the U. S. Army.

Exogenous or Endogenous Reinfection

The occurrence of exogenous or endogenous reinfection has not been clearly defined, but evidence of its occurrence is accumulating. Indeed, it would appear that all cases of chronic progressive histoplasmosis really are cases of relapse or reinfection since the tendency in cases of other types of the disease is for recovery or dissemination to occur soon after the primary infection. In a number of cases of chronic progressive histoplasmosis, follow-up studies, which sometimes included autopsies, have revealed evidence of healed calcified lesions as well as the active lesions which caused death. In some cases, these calcified lesions have been known to have been present for several years before the chronic progressive type of the disease became evident. The presence of tuberculosis sometimes has been ruled out by negative tuberculin tests or by

negative cultures made with material obtained at autopsy.

Since it is well known that reinfection has a tendency to occur in cases of tuberculosis, it would be surprising if it did not occur in cases of histoplasmosis. In a number of cases, reinfection apparently has occurred in children. In these cases, there has been calcification or other evidence of healed lesions as well as active pneumonic infiltration, which usually was peripheral to the calcification and was accompanied by rather severe symptoms which lasted as long as several months. In these cases, clearing of the lungs occurs eventually, but serologic tests for histoplasmosis usually are positive. These seem to be cases of reinfection superimposed on old healed disease.

Other Manifestations

Pleurisy and thin-walled cavities of the coccidioidal type seem to occur only rarely in cases of histoplasmosis. Erythema nodosum, which occurs commonly in cases of primary coccidioidomycosis, has not been reported to have occurred in cases of histoplasmosis.

Other atypical types of the disease such as chronic lesions of the skin have been described by Parsons and Zarafonetis,[2] and penile lesions have been described by Curtis and Grekin.[23] These types appear to be rare, and their incidence is not known.

Sequelae of Healing

Attention should be called to the development of the so-called middle lobe syndrome coincident with the healing of enlarged hilar lymph nodes. The fibrosis and calcification in the nodes apparently constrict the bronchus and thus cause atelectasis and subsequent infection of the collapsed lobe. In cases in which this syndrome occurs, serologic tests often are negative, and pathologic examination and cultures of the excised lung frequently fail to disclose *H. capsulatum*. The incidence of the middle lobe syndrome in cases of histoplasmosis has not been determined, but I have seen a number of cases in which it has occurred.

The coughing up of broncholiths occasionally occurs in cases in which positive histoplasmin skin tests indicate that infection with *H. capsulatum* has occurred previously. Chest roentgenograms usually reveal large, calcified hilar lymph nodes. By the time broncholithiasis occurs, serologic tests are usually negative. Remember that pulmonary and/or nodal calcification is present in about one-third of the cases in which a histoplasmin skin test is positive, but is present in only one-tenth of the cases in which a tuberculin test is positive.

Value of Serologic Tests

I believe that serologic tests are invaluable in the diagnosis of histoplasmosis. These tests are positive only during the acute stages of the disease, and the titers tend to fall when healing of the lesions occurs. The titer usually is elevated for as long as a year, but it may be elevated for as long as five to seven years in cases in which severe pulmonary damage has occurred or in cases in which enlarged lymph nodes heal slowly. Serologic tests usually continue to be positive in the chronic progressive type of the disease. In cases of proved histoplasmosis, serologic tests occasionally continue to be negative for unknown reasons.

In my experience, the precipitin test usually has been the first to become positive and the first to show a fall in titer. Complement fixation tests may be performed by two methods: (1) by using an antigen made from the yeast phase of a culture, and (2) by using an antigen made with histoplasmin. The results of these two tests often are dissimilar; occasionally, only one of the tests is positive. It, therefore, is extremely useful to have the precipitin test and the two complement fixation tests performed on any specimen of serum.

Serologic tests also are useful prognostically.[24] Persistently high or rising titers or a failure of the precipitins to disappear is a bad prognostic sign. Serologic tests may be obtained through the departments of health in different states. The use of paired specimens of serum, one obtained early and the second one three to four weeks later, has been mentioned previously.

Other Laboratory Aids

It should be emphasized that isolation of *H. capsulatum* by culture and its recognition

in pathologic specimens are not especially difficult for trained personnel. However, this fungus can easily be overlooked by competent pathologists who are unacquainted with its appearance or by laboratory workers who do not employ mycologic methods for the identification of fungi.

Treatment

No satisfactory treatment has been established, although new drugs are being tried at present.[25]

Summary

An attempt has been made to outline a classification of histoplasmosis. It should be emphasized, however, that this classification is tentative and is subject to revision as additional clinical knowledge of the disease is acquired. The similarities of this disease and coccidioidomycosis and tuberculosis have been discussed. The necessity for physicians to suspect the presence of this disease has been stressed, and the methods of diagnosis have been discussed.

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CHANGES IN INTERSTATE ASSEMBLY PROGRAM

Address: The Problem of Ulcerative Colitis.
Joseph B. Kirsner, M.D.
Wednesday, October 24, 3:00 P.M. from Monday, October 22, 3:30 P.M.

Address: Drug Therapy in Hypertension
Irvine H. Page, M.D.
Monday, October 22, 3:30 P.M. from Wednesday, October 24, 3:00 P.M.

Dr. Austin B. Chinn, Associate Professor of Medicine, Western Reserve University School of Medicine, Cleveland, will substitute for Dr. Kirsner in panel on Gastrointestinal Bleeding, Monday, October 22 at 1:30 P.M.

Nonspecific Tenosynovitis With Effusion at the Ankle

EMIL D. W. HAUSER

Chicago

EMIL D. W. HAUSER

LAPIDUS and Seidenstein[1] in 1950 reported three cases of chronic nonspecific tenosynovitis with effusion about the ankle. They considered it a rare condition. I have treated 12 such cases; in each of these cases there was chronic inflammation together with effusion of the tendon sheaths at the ankle.

No bacteria or virus is involved in this type of tenosynovitis, nor is there any history of direct trauma. The findings consist of slight pain and tenderness over the tendon sheath itself, and a definite synovial effusion. The condition is usually associated with chronic foot strain.

One must differentiate nonspecific tenosynovitis first from tenosynovitis associated with rheumatoid arthritis; signs of infection or joint involvement are not present, as in the latter. The absence of any tuberculous lesion in the body helps distinguish it from tuberculous tenosynovitis. In peritendinitis crepitans, the effusion is absent and the symptoms usually are directly related to mechanical strain, local irritation or infection; a great number of such cases occur in the early days of military training after strenuous hikes.[2] In the stenosing type of tenosynovitis one finds thickening of the tendon as well as constriction of the sheath, which gives rise to a trigger action. Anomalies of the tendon have been described in cases of tenosynovitis of the tibialis posterior muscle.[3]

Ten of my patients were women and two were men. Their ages ranged from 23 to 60 years. All the women were housewives, three of whom also did office work and one factory work. The two men did heavy factory work. Duration of the illness varied from six months to 11 years.

The tendon sheaths of the peroneal muscles were involved in five cases. In five other cases the condition affected the tendon sheath of the tibialis anterior. The tendon sheath of the extensor digitorum longus muscle was in-

volved in two, and those of the extensor hallucis longus and tibialis posterior in one case each. In one case, three tendon sheaths were involved (figure 1).

Lapidus and Seidenstein reported relief of local symptoms following removal of the tendon sheath. I treated all 12 of my patients by injecting HYDROCORTONE® directly into the involved tendon sheath. In one instance, surgery had been carried out previously and the condition had recurred.

I operated on one patient to establish the diagnosis. I removed the tendon sheaths of the peroneal, tibialis anterior and tibialis posterior muscles. The pathologist reported that the synovial tissue showed chronic inflammatory reaction consisting of infiltration by chronically inflamed cells with increased fibrosis. The diagnosis was chronic synovitis. Cultures were negative.

The number of injections of Hydrocortone necessary for cure varied from 2 to 31. The duration of the condition did not influence the length of time it took to obtain a cure. There seemed to be a direct ratio between the time required to cure the tenosynovitis and that necessary to relieve the chronic foot strain. Treatment of the chronic foot strain consisted of adhesive strapping, pads in the shoes, and corrective shoes with Thomas heels and comma-shaped bars. Correct gait was taught until normal gait was re-established. This conservative treatment has the advantage that the patients remain ambulant and continue their work during recovery.

Case Reports

Case 1—A 30 year old housewife came to me because of painful feet. I made a diagnosis of pes valgoplanus with contracted toes and hallux valgus with bursitis, and prescribed corrective shoes and gait training. She got along quite well for eight months. Then she returned with swelling on the dorsum of the right foot. I made a diagnosis of nonspecific tenosynovitis with effusion of the tendon sheath of the extensor hallucis longus. All attempts to relieve the swelling by means of strapping and physical therapy were of no avail. A year later, Hydrocortone became available and I injected 1 cc. into the involved tendon sheath. There was immediate improvement. Treatment continued and the patient made a complete recovery. When last seen a year and a half later she had remained well.

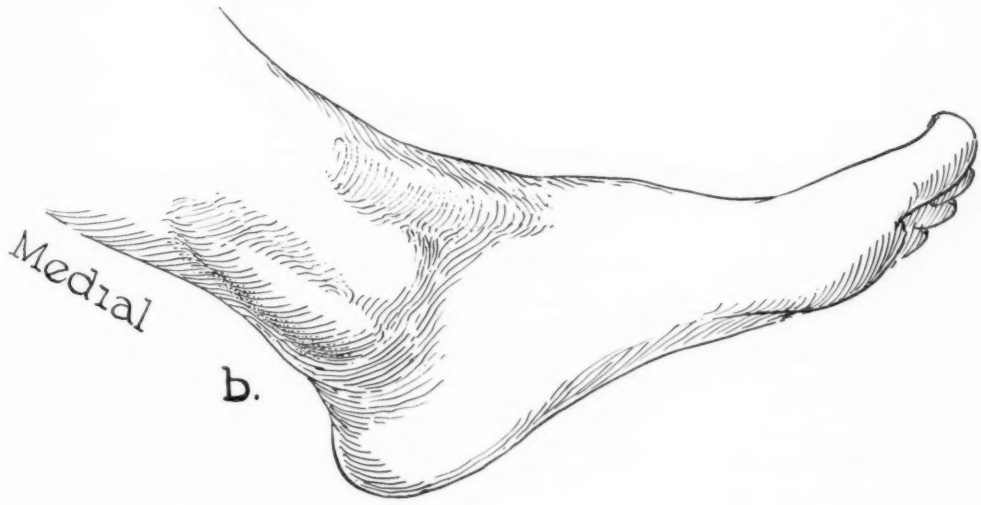
Case 2—A 44 year old stenographer complained of pain and swelling of the right ankle of 11 years' duration. Preceding their onset, she had been in an automobile accident. She had settled with the insurance company but the swelling had persisted. Examination revealed tenderness with increased fluid over the tendon sheath of the tibialis anterior muscle. I prescribed corrective shoes, and the pain subsided but the swelling of the sheath persisted. I then injected the tendon sheath with Hydrocortone. Improvement occurred at once and after 14 injections the symptoms had completely subsided.

Case 3—A 39 year old doctor's wife had had pain in the left foot and ankle for two years. It had started suddenly, with swelling. She wore arch supports, without relief. Examination showed swelling of the tendon sheath of the left tibialis anterior muscle, and pes valgoplanus of the left foot. I prescribed corrective shoes and gait training. She had relief of the foot pain but the swelling of the tendon sheath persisted. I then injected the tendon sheath with Hydrocortone and after two injections the swelling disappeared.

Case 4—A 46 year old woman, a factory worker, came to me with the complaint of pain in the right foot of one year's duration. Examination disclosed pronation grade 2, valgus grade 2, splayfoot grade 2, and tenderness and increased fluid in the tendon sheath of the common extensors of the toes. I made a diagnosis of tenosynovitis with effusion of the extensor tendon. Treatment consisted of injections of Hydrocortone, strapping of the foot and corrective shoes. She had immediate relief. Three months after treatment was started, she was seen because of a mild foot strain; the tendon sheath was normal.

Case 5—A 50 year old housewife complained of pain and swelling of the right ankle. A year previously, she had had a similar condition which had subsided spontaneously. She also complained of metatarsal pain. Ex-

FIGURE 1. a. Tenosynovitis with effusion of the tendon sheath of the peroneal muscle. b. Tenosynovitis with effusion of the tendon sheaths of the tibialis anterior and tibialis posterior muscles.



amination showed tenderness and swelling over the tendon sheath of the tibialis anterior muscle, and pes valgoplanus grade 3. I injected Hydrocortone into the tendon sheath, strapped her ankle and prescribed corrective shoes. After three injections her symptoms were entirely relieved.

This was a case of tenosynovitis with effusion in which there was foot strain. Use of Hydrocortone and correction of the foot strain gave quick relief without recurrence.

Case 6—A 60 year old housewife complained of a painful left foot and ankle. The ankle felt as though it were sprained and was swollen. Examination revealed swelling of the peroneal tendon sheath and pes valgoplanus grade 2. The foot was strapped, corrective shoes were prescribed and Hydrocortone was injected into the tendon sheath. She had 12 injections of Hydrocortone. She was unable to follow through consecutively, and there were long periods when treatment was not carried out. She was seen a year after treatment was started and had recovered completely.

Case 7—A 40 year old male factory worker came to me complaining of pain and swelling of the right ankle. Two months previously, the lateral aspect of his right leg and ankle had been struck by a falling piece of iron. X-rays were negative. Some pain developed in the anterior surface of the ankle. A cast was applied, without benefit. When I saw him, he had tenderness and swelling over the tendon sheaths of the common extensor muscles of the toes. He had a weak foot with foot strain. I injected the sheath with Hydrocortone seven times, strapped his ankle and prescribed corrective shoes. Two months later he had complete relief, and was able to carry out all normal duties.

Case 8—A 35 year old male factory worker was referred to me because of pain and swelling in his right ankle. He gave a history of an injury while at work, involving a direct blow to the lateral side of the ankle with some lacerations. This had healed, and four weeks later the ankle pain and swelling had appeared. X-rays showed normal findings. Examination revealed tenderness and swelling over the peroneal tendon sheath and pes valgoplanus grade 2. I made a diagnosis of foot strain with tenosynovitis of the peroneal tendon sheath. I injected the tendon sheath with Hydrocortone at weekly intervals for two months. His foot was strapped and corrective shoes were prescribed. When last seen for a check up six months after his original examination, his symptoms had completely subsided. He was able to work without difficulty.

The patients in cases 7 and 8 gave a history of trauma preceding the tenosynovitis with effusion. The tenosynovitis developed some time after the injury. It offered a problem to the attending surgeon in that the tenosynovitis was due to foot strain rather than directly to the injury. Injection of Hydrocortone into the tendon sheath and correction of the foot strain resulted in cure.

Case 9—A 51 year old housewife complained of a painful heel of four months' duration. Tenderness over the os calcis, pronation grade 3, valgus grade 3 and splayfoot grade 3 were noted. There was swelling with increased fluid over the peroneal sheath of the right foot. She had five injections of Hydrocortone. The foot was treated with adhesive strapping and corrective shoes. When the patient was last seen six months later the foot symptoms were relieved and the tendon sheath was normal.

Case 10—A 43 year old office worker had pain in the left foot and ankle of two years' duration. The onset was insidious and the condition became progressively worse. The pain was not severe but the swelling around the ankle was troublesome. There was some swelling at the ankle joint itself, and synovitis of the tendon sheaths of the peroneal, tibialis anterior and tibialis posterior muscles, with effusion.

With the two year history and the lack of response to previous treatment, I was concerned about the possible presence of a synovioma. The patient was admitted to Passavant Hospital where the tendon sheaths were removed and a section of synovial tissue was removed from the ankle joint. The removed tissue showed chronic inflammatory reaction consisting of infiltration of chronic inflammatory cells with increased fibrosis. The patho-

logic report was that of chronic synovitis. There was some persistence of swelling at the ankle joint. The ankle was injected with Hydrocortone at two week intervals. The patient was last seen two years later. The tenosynovitis was completely relieved. There was slight thickening of the ankle.

Case 11—A 55 year old office worker complained of painful feet and swelling of the left ankle. Examination revealed swelling over the peroneal tendon sheath with effusion in the sheath and tenderness over this area, pronation grade 3, valgus grade 3, splayfoot grade 4 and contracted toes grade 4. I made a diagnosis of pes valgoplanus with contracted toes, foot strain and nonspecific tenosynovitis with effusion of the peroneal tendon sheath of the left foot. I injected Hydrocortone and the condition improved. She continued to be on her feet too much. I applied a Gibney bandage to the left ankle and then prescribed corrective shoes. After 31 injections of Hydrocortone the swelling was entirely relieved and no longer recurred.

This case demonstrates the need for correcting foot strain and pes valgoplanus along with using Hydrocortone to cure a nonspecific tenosynovitis with effusion.

Case 12—A 23 year old housewife had tenosynovitis of both ankles of five years' duration. The tendon sheath of the left tibialis anterior muscle had been removed four years previously, and the condition had recurred. I injected 2 cc. of Hydrocortone into the tendon sheath, and there was prompt response. After four injections she had complete relief without recurrence.

Summary

Nonspecific tenosynovitis with effusion occurs relatively infrequently at the ankle. It is associated with foot strain and pes valgoplanus. The use of Hydrocortone and correction of the foot strain will result in cure. Twelve cases are reported.

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MEETINGS *and Postgraduate Courses*

Tufts University School of Medicine, Boston: Postgraduate courses for general practitioners and internists to be presented at the New England Medical Center, 1956-1957:

Electrocardiography I, December 17-21
Electrocardiography II, May 13-15
Rheumatic diseases, November 1-3
Vascular diseases, November 16-17
Dermatology, November 23-24
Fluid and electrolyte disturbances, January 10-12
Diabetes, February 7-9
Orthopedic surgery, February 15-16
Rehabilitation, February 28-March 2
Office gynecology, March 7-9
Pediatrics, March 21-23
Hematology, April 4-6
Cardiology, April 11-13
Neurology, May 1-4
Allergy, May 9-11
Selected chest radiology, May 17-18

Tulane University School of Medicine, New Orleans: Continuation courses to be offered by Division of Graduate Medicine, 1956-1957:

Diagnostic radiology, November 8-9
Electrocardiography, December 3-14
Ocular pathology, December 3-8
Infectious diseases in pediatrics, February 4-9
Surgery of the hand, March 21-23
Industrial medicine, April 4-5
Hematology, April 10-12

For detailed information write: Director, Division of Graduate Medicine, 1430 Tulane Avenue, New Orleans 12, Louisiana.

Thorazine (Chlorpromazine) as a Complicating Factor in the Diagnosis of Extrahepatic Obstructive Biliary Disease

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JAUNDICE is a physiologic entity that is startling to the patient and physician alike. Fundamentally, it is a bilirubinemia of a degree sufficient to stain the skin and mucous membranes. Since bilirubin is a degradation product of red cell destruction, jaundice may be caused by either an overproduction or failure of excretion of this pigment.

It has become customary to classify jaundice, perhaps somewhat loosely, into two types, namely, medical and surgical. The latter type signifies an extrahepatic obstructive phenomenon. In cases in which jaundice is due to excessive destruction of red cells and the consequent overproduction of bilirubin, a type of medical jaundice, the diagnosis is readily established. It becomes more difficult to distinguish jaundice due to intrahepatic lesions, such as hepatitis caused by viral or purulent infections, other parenchymal cellular disease, or cirrhosis, from the strictly surgical (extrahepatic) type of jaundice. The treatment of the two types is entirely different.

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TABLE 1

CLINICAL DATA

CASE	SEX	AGE, YR.	ADMINISTRATION OF THORAZINE			JAUNDICE		DIAGNOSIS
			Days of therapy	*Maximal daily dose, mg.*	*Total dose, mg.*	*Onset, day**	*Clearance, weeks*	
1	M	61	9	150	1,425	9	9-12	Postgastrectomy distress (2 mo.)
2	F	54	48	150	4,125	34	10-16	Manic-depressive psychosis
3	M	72	14			21	?	Prostatic carcinomatosis
4	F	27	28	125	3,500	28	10	Paranoid state
5†	F	53	20 6	200 200	3,700 1,200	18 6	3	Agitated depression
6	F	54	21	400	4,300	21	3-4	Paranoid state
7	M	51	23	150	3,450	23	3-8	Refractory behavior; tuberculosis

*After administration of Thorazine was started.

†Two courses were used in this case. The second course was started seven months after the first one was completed.

A correct diagnosis logically must precede proper therapy. Diagnostic procedures for distinguishing the different types of jaundice are many and well known. There are a multitude of biochemical tests based on widely different principles, but when these tests are employed singly or in groups the results are difficult to evaluate. Roentgenography is of little value in the diagnosis of jaundice. At times, even a carefully taken history and a well-conducted physical examination may be misleading.

Further confusion has been added by the recent introduction of the product THORAZINE® (chlorpromazine). This drug has a selective depressant action on the central and autonomic nervous systems. The physician must be aware that this drug may cause such complications as agranulocytosis, skin eruptions and hypotensive effects, and that it may cause potentiation of other depressant agents. The surgeon particularly must be aware that it may cause jaundice which closely simulates that due to extrahepatic obstructive biliary disease.

Clinical Material

Seven cases in which jaundice was associated with Thorazine medication have been observed at the University hospitals and the Veterans Administration Hospital in eight months. The presence of this complication was suspected in another case, but this case was rejected from consideration because of insufficient data. In the differential diagnosis in the seven cases, we considered the possibility that surgical obstructive jaundice might have occurred at some time during the period of hospitalization. In three of the cases, the jaundice was the factor that motivated the surgeon to perform an exploratory laparotomy.

Table 1 shows the clinical data in the seven cases. As a result of exploratory laparotomy or subsequent observation, it is known that obstructive extrahepatic biliary disease was not present in six of the seven cases. Although the data in the remaining case (case 7) are incomplete, clinical appraisal has indicated that obstructive extrahepatic biliary disease was not present.

Case 1—A 61 year old man who was suffering from distress two months after gastrectomy received 1,425 mg. of Thorazine in nine days. The peak daily dose was 150 mg. Jaundice developed on the ninth day, and the administration of Thorazine was discontinued. An exploratory laparotomy was performed because of what was considered to be unexplained obstructive jaundice. The extrahepatic biliary tree was not obstructed. The jaundice disap-

peared in 9 to 12 weeks after its onset.

Case 2—A 54 year old woman who was being treated for manic-depressive psychosis received 4,125 mg. of Thorazine in 48 days. The peak daily dose was 150 mg. Jaundice developed on the thirty-fourth day, and the prodromal symptoms suggested the presence of cholangitis. Since the patient was known to have cholecystolithiasis, the presence of a stone in the common bile duct was suspected. An exploratory operation revealed that the common bile duct was not obstructed. The jaundice subsided in 10 to 16 weeks after its onset.

Case 3—A 72 year old man received an unknown amount of Thorazine in two weeks. Painless jaundice developed one week after the administration of the drug was discontinued. The diagnosis was prostatic carcinomatosis. Operation was performed because it was thought that the patient had a neoplastic obstruction of the extrahepatic biliary system. Exploration of the common bile duct did not reveal any obstruction. The patient was last observed 13 weeks after the onset of the jaundice, and the jaundice still was present.

Case 4—A 27 year old woman who was being treated for a paranoid state received 3500 mg. of Thorazine in 28 days. The peak daily dose was 125 mg. Jaundice developed on the twenty-eighth day and disappeared in approximately 10 weeks. Cholecystography did not disclose any abnormality.

Case 5—A 53 year old woman who was being treated for agitated depression received 3700 mg. of Thorazine in 20 days. The peak daily dose was 200 mg. She became jaundiced on the eighteenth day. The jaundice disappeared subsequently, but further details are not available. Seven months later, 1200 mg. of Thorazine was administered in six days. The peak daily dose during this course was 200 mg. Jaundice again became evident, and transient albuminuria occurred. The jaundice disappeared in three weeks, and cholecystography did not disclose any abnormality at that time.

Case 6—A 54 year old woman who was being treated for a paranoid state received 4300 mg. of Thorazine in 21 days. The peak daily dose was 400 mg. Jaundice appeared on the twenty-first day and disappeared by the fourth week. Cholecystography did not reveal any abnormality.

Case 7—A 51 year old man who was a patient in a tuberculous sanatorium received 3,450 mg. of Thorazine in 23 days because of refractory behavior. The peak daily dose was 150 mg. Jaundice appeared on the twenty-third day and disappeared in three to eight weeks. Cholecystography failed to visualize the dye. Further study was not possible.

Pathologic Findings

An exploratory laparotomy was performed in three cases. In these cases, gross inspection of the liver revealed a tense Glisson capsule, which indicated parenchymal swelling. Staining due to bile stasis was present. In the case in which cholecystolithiasis was known to be present, palpation revealed that the capsule was coarsely granular. Tissue for histologic study was obtained in four cases, and biopsy was performed on more than one occasion in two cases.

The histologic findings were consistent and rather severe, although they were by no means pathognomonic of this entity. Microscopic examination revealed bile pigment in many parenchymal cells, inspissated bile casts in the canaliculi, and mild to very active hyperplasia of the Kupffer cells. Many of the parenchymal cells were swollen. There was mild to rather marked variation in the size of the nuclei. Mitosis occasionally was evident, and numerous binuclear or multinuclear cells were observed. Periportal round cell infiltration usually was present to a moderate degree and tended to fade into the liver lobules. Figures 1, 2 and 3 illustrate the hepatic changes.

Comment

On clinical appraisal it generally was noted that, one week before the icterus appeared, the patients felt ill and had pain or discomfort in the epigastrium or in the right upper quadrant of the abdomen. Fever occasionally was present. After icterus appeared, the liver was swollen and tender, and the patients complained of generalized pruritus.

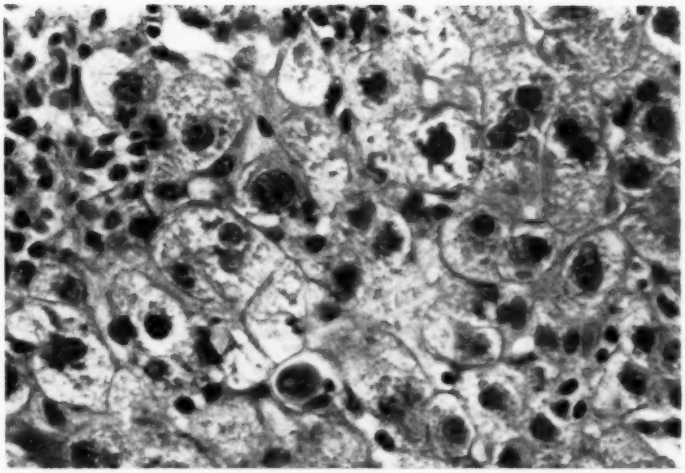

FIGURE 1. Photomicrograph of section of liver (case 1) showing round cell infiltration, binuclear cells, swelling of the liver cells, and degenerating nuclei. Bile pigment may be seen in the canaliculi, in the liver cells and in phagocytes in the sinusoids. (x490)

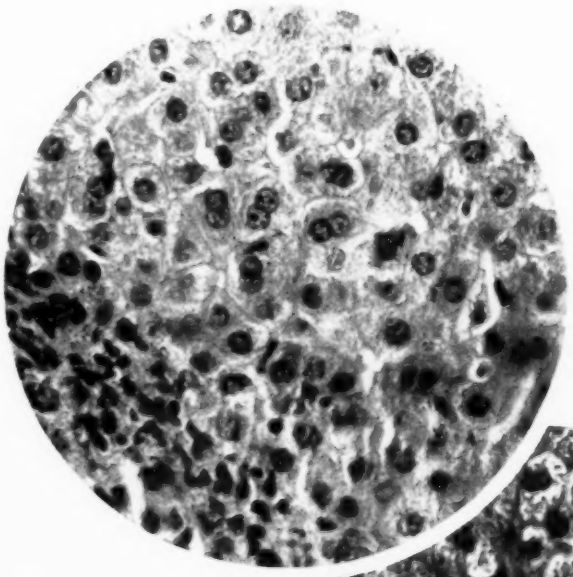

FIGURE 2. Photomicrograph of tissue obtained by needle biopsy two weeks after the onset of jaundice in case 4. Inflammatory infiltration, binuclear cells, reticulo-endothelial hyperplasia, and variation in the size and staining qualities of the nuclei may be seen. Inspissated bile is present in the canaliculi, and pigment may be seen in the liver cells. (x490)

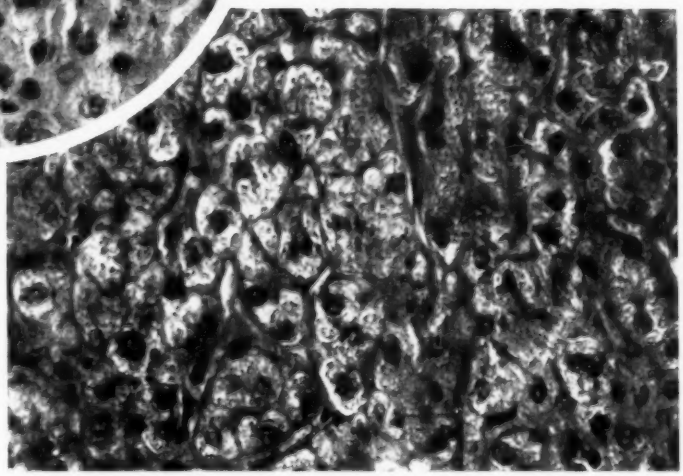

FIGURE 3. Photomicrograph of tissue obtained by needle biopsy 10 weeks after the onset of jaundice in case 4. The jaundice has cleared, and only mild residual damage of the parenchymal cells and inflammatory changes persist. (x490)

TABLE 2

RESULTS OF LIVER FUNCTION TESTS

CASE	SERUM BILIRUBIN	CEPHALIN-CHOLESTEROL FLOCCULATION	SERUM ALKALINE PHOSPHATASE	SERUM CHOLESTEROL	PLASMA PROTEIN	ALBUMIN-GLOBULIN RATIO OF PLASMA
1	Abnormal	Abnormal	Abnormal		Normal	Normal
2	Abnormal	Abnormal	Abnormal	Abnormal	Normal	Normal
3	Abnormal	Abnormal	Abnormal	Abnormal	Low	Normal
4	Abnormal	Abnormal	Abnormal	Abnormal	Normal	Normal
5	Abnormal	Normal	Abnormal	Abnormal	Normal	Normal
6	Abnormal	Abnormal	Abnormal	Abnormal	Normal	Normal
7	Abnormal	Abnormal	Abnormal	Abnormal	Normal	Normal

Our data do not permit a study of the incidence of jaundice in cases in which Thorazine is administered. Hodges and LaZerte[1] said that jaundice occurred probably more frequently than published reports indicated. Lehmann and Hanrahan[2] said that it occurred in 3 of 71 cases, Azima and Ogle[3] said that it occurred in 5 of 100 cases, and Moyer and his associates[4] said that it occurred in one of more than 500 cases. Lomas, Boardman and Markowe[5] said that toxic reactions occurred in 59 (7.4 per cent) of 800 cases in which this drug was administered, and they said that jaundice occurred in 11 of the cases.

Authors do not agree on the significance of this manifestation of hepatic dysfunction. Cohen and Archer,[6] who observed jaundice in 5 of more than 800 cases in which Thorazine was administered, thought that it was of little significance, while Lomas, Boardman and Markowe,[5] who observed this complication in 11 of 800 cases, thought that it was potentially grave.

We believe that liver damage is definite in cases of this type. Although the mechanism of liver damage is not clear, it is suggested that Thorazine has a selective toxic action on the liver in some cases. We have not observed any case in which the transient use of this drug has caused jaundice. The duration of medication appears to be of greater importance than the size of the daily dose. The presence of specific predisposing factors has not been noted.

We have observed a case in which transient albuminuria without jaundice developed after Thorazine had been administered for 10 days. The albuminuria disappeared although the administration of the drug was continued. Albuminuria also was present in case 5, and this suggests that renal damage may occur. In this case, the albuminuria occurred during the second episode of jaundice, which occurred promptly when relatively small doses of the drug were administered seven months after the first episode. This single case cannot refute the observation of other authors[6] that Thorazine may be administered again after the subsidence of jaundice, but it would suggest caution in resuming its administration.

In all of the cases in our series, the values for the serum bilirubin, serum alkaline phosphatase and serum cholesterol were increased at the onset of the jaundice or shortly thereafter (table 2). The value for the serum bilirubin returned to normal in 3 to 16 weeks. The values for the serum alkaline phosphatase and serum cholesterol tended to be most tardy in returning to normal. In one case, they remained elevated for nine months. The cephalin-cholesterol flocculation was increased in six of the seven cases. In general, the increase persisted for 12 weeks, and in one case it lasted for nine months. Other flocculation tests were used less extensively. In our experience, Thorazine medication has not caused these biochemical abnormalities unless it has been complicated by jaundice. The jaundice caused by Thorazine is of particular significance since the clinical course and laboratory data mimic those of a true obstructive biliary lesion.

We have observed another case which might

be added to this series. The patient was a 69 year old woman. Jaundice developed after Thorazine had been administered for nine days, and the symptoms, signs and laboratory data suggested the presence of an extrahepatic obstructive biliary lesion. Four weeks after the jaundice developed, an exploratory laparotomy disclosed a primary carcinoma of the extrahepatic biliary tree which had spread through the biliary radicles into the liver.

It has become obvious that the surgeon cannot conscientiously wait for jaundice to subside in all cases, for the presence of a true obstructive lesion cannot be conclusively excluded and the most propitious time for treatment may have passed if operation is delayed.

Summary and Conclusions

1. Thorazine, a recently introduced and widely used drug, has been associated with and may cause hepatic damage which may mimic an extrahepatic obstructive lesion.

2. To avoid patient disservice, the surgeon at times may be forced to perform an exploratory operation.

3. In cases in which jaundice is associated with the administration of Thorazine, the values for the serum bilirubin, serum alkaline phosphatase and serum cholesterol are increased and tend to be tardy in returning to normal. This is particularly true of the serum alkaline phosphatase. The cephalin-cholesterol flocculation usually is increased and also is slow in returning to normal.

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Postgraduate Clinical NOTES

54. VITAMINS IN PREGNANCY

During certain periods of life there is an increased demand on the part of the body for vitamins. The most important of these periods is pregnancy. From the original observations that beriberi and night blindness occurred more commonly in pregnant women, it has gradually become recognized that there is an increased requirement for all the vitamins during pregnancy. Some obstetricians are even inclined to attribute some of the common disorders of pregnancy, such as uterine hemorrhage, to vitamin deficiency (McIlroy, 1935). Be that as it may, in recent years the supplementation of the diet of the expectant mother with an adequate supply of vitamins has become a recognized feature of antenatal hygiene. There is a possible danger that, with the increasing scepticism concerning the value of vitamins, this precaution may cease to be taken.

D. H. M. Woolam and J. W. Miller, Role of vitamins in embryonic development, *British Medical Journal*, June 2, 1955, pp. 1262-1264

Late Electrocardiographic Changes in Acute Myocardial Infarction — a Problem in Diagnosis

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MODERN diagnosis of acute myocardial infarction depends largely on the electrocardiogram. The advantage of objective evidence to substantiate a conclusion cannot be denied. When one is confronted with an acute chest condition, an acute abdominal episode or unexplained shock or collapse, the electrocardiograph may yield the answer. This is not to dispute that the diagnosis of acute infarction often can be ascertained fairly well on clinical grounds alone, or that a correlation of history and physical findings with the electrocardiogram is always imperative.

It has been reported that 90 per cent of persons with acute myocardial infarction have abnormal electrocardiograms.[1] How many such electrocardiograms are typical or diagnostic is not definitely established. Unquestionably the introduction of multiple chest leads and unipolar leads has increased their accuracy.

Recently I observed three cases in which myocardial infarction was suspected on the basis of clinical findings, and electrocardiographic substantiation was desirable. Serial tracings in these cases had to be continued to the sixth, twelfth and twentieth days respectively before diagnostic tracings were recorded. Thus the importance of serial graphs is realized.

Barker[2] commented on the danger in basing a diagnosis on a single electrocardiogram taken on hospital admission. Diagnostic signs may be absent, and if further tracings are not made the patient may be released. Rosenbaum[3] warned that the physician may be falsely reassured when the first tracing is normal or the second shows no change. He emphasized that changes may be delayed and serial tracings should be continued.

Standard texts on cardiology and electrocardiography tell us that electrocardiographic changes in acute myocardial infarction may occur a few hours after its onset or may be delayed several hours or days or even up to three weeks. A review of the literature revealed only one report of a specific study in this respect. The authors, Feldman, Raskin

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and Wolff,[4] found that only 34 per cent of the first tracings taken within the first 24 hours in 200 consecutive cases of acute myocardial infarction were diagnostic.

In an attempt to determine in how many instances electrocardiographic changes are delayed in acute myocardial infarction, and for how long, a study of consecutive hospital admissions during the course of one year was made. Included were only those cases in which the diagnosis appeared to be definite according to the records. All the tracings were reviewed and only those in which there appeared QRS changes were accepted as definitely diagnostic. Changes in the RST segment alone or with abnormalities in T wave were classed as suspicious. The occurrence of T wave changes alone was listed as nonspecific. In addition, other laboratory findings were correlated, namely, elevation of white cell count and sedimentation rate, and the occurrence of fever. In general, these tests substantiated the electrocardiographic findings but these are not included here.

The group studied consisted of 145 cases, of which 33 patients were women (23 per cent) and 112 were men (77 per cent) (table 1). Their ages ranged from 33 to 86 years, averaging about 60 years. There were 43 deaths, a mortality rate of 30 per cent; 16 or 37 per cent occurred within the first 24 hours after admission.

In 119 cases the records included electrocardiograms suitable for analysis. All tracings were separated as to time of recording; each was reviewed and the conclusions were recorded. Electrocardiograms were made within 24 hours after the patient's admission to the hospital in 87 cases (table 2). A definite diagnosis of acute infarction was possible in 42 cases. Twenty tracings were suspicious, 17 were nonspecific and eight were within normal limits. Therefore, 48 per cent or a little less than half of the electrocardiograms recorded on the first hospital day indicated a definite diagnosis of acute myocardial infarction.

Initial electrocardiograms were made on the second day after admission in 24 cases. They were diagnostic in 15, suspicious in five, nonspecific in two and normal in two. Combining the two groups, we find that 52 per cent of tracings made within the first two days after admission to the hospital were definitely diagnostic of infarction.

In five instances the initial electrocardiographic records were made on the third hospital day. Three were diagnostic, one was suspicious and one was nonspecific. Of two initial records made on the fourth day, one was diagnostic and one suspicious. In one case the electrocardiogram was not made until the thirteenth hospital day and at that time showed definite changes.

Thus, of all the initial tracings, 62 were diagnostic, 27 suspicious, 20 nonspecific and 10 within normal limits.

Then reviewed were 57 cases in which the initial tracings were not diagnostic (table 3). Repeated tracings became diagnostic in 22 of the 27 cases in which the initial electrocardiograms were suspicious. In one case the tracing remained suspicious, and in four instances tracings were not repeated. In 20 cases with initially nonspecific tracings, diagnostic rec-

TABLE 1

SUMMARY OF CASES OF MYOCARDIAL INFARCTION STUDIED

Total cases, 145
Age range, 33 to 86 years (average about 60)
Ratio of women to men, 33 to 112 (23% to 77%)
Mortality rate, 30% (43 deaths)
Deaths within first 24 hours, 16 (37%)

TABLE 2

RESULTS OF INITIAL ELECTROCARDIOGRAPHIC TRACINGS IN 119 CASES OF MYOCARDIAL INFARCTION

EKG RESULT	HOSPITAL DAY					TOTAL
	1	*2*	*3*	*4*	*13*	
Diagnostic	42	15	3	1	1	62
Suspicious	20	5	1	1		27
Nonspecific	17	2	1			20
Normal	8	2	—	—	—	10
	87	24	5	2	1	119

TABLE 3

RESULTS OF FURTHER ELECTROCARDIOGRAPHIC STUDIES IN 57 CASES IN WHICH INITIAL TRACINGS WERE NOT DIAGNOSTIC

RESULT OF FURTHER STUDY	INITIAL EKG RESULT			TOTAL
	Suspicious	*Nonspecific*	*Normal*	
Diagnostic	22	9	4	35
Suspicious	1			1
Nonspecific		4		4
Normal			3	3
EKG not repeated	4/27	7/20	3/10	14/57

ords were obtained in nine while four showed no change, and in the remaining seven serial records were not made. Subsequent tracings became diagnostic in four of the 10 cases in which original electrocardiograms were normal; three remained normal and in three cases the tracings were not repeated.

It is necessary to explain at this point that in instances in which the electrocardiogram did not become definitely diagnostic of myocardial infarction the reason may be that serial records were not continued further, as in eight of the cases listed, or that the electrocardiogram was not repeated or could not be, as in 14 instances. Ten of the latter patients died, two were transferred to other institutions, and in the remaining two cases the reasons for not repeating the electrocardiographic tracing were not known.

To demonstrate further the necessity of making serial tracings to obtain a definite diagnosis, those cases were tabulated in which

TABLE 4

DELAYED ELECTROCARDIOGRAPHIC CHANGES IN 11 CASES OF MYOCARDIAL INFARCTION

CASE	HOSPITAL DAY															
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*20*
1	?		?											D		
2	?	?		?			?				D					
3	N			N		D										
4	N		N			N					D					
5	?		?			D										
6		?					?							D		
7		?		?				?				D				
8	?	?	D													
9	?						?							D		
10	?						?						D			
11	N								N							D

?—Indefinite.
N—Normal.
D—Diagnostic.

a definite conclusion was reached but more than one repeat tracing had to be done (table 4). This group comprised 11 cases. Note in table 4 that the time interval between hospital admission and the appearance of electrocardiographic changes ranged from the third to the twentieth day and that they were indefinite as late as the ninth day after admission.

When correlating further facts elicited from this study, it was determined that the patient's age and sex and the site of the infarct had no bearing on the delayed appearance of diagnostic electrocardiographic changes. Certain well-known factors such as the size of the infarct, the position of the heart, the leads used, number of tracings and time of recording still are determining factors which influence electrocardiographic results.

Summary

1. Diagnosis of acute myocardial infarction depends heavily on the electrocardiogram.

2. In a study of 145 consecutive hospital admissions, 48 per cent of tracings made on the first day of hospitalization were definitely diagnostic.

3. Fifty-two per cent of all initial records were diagnostic. By serial recording, the diagnostic yield was increased to 82 per cent.

4. Failure to secure conclusive records is explained by the failure to obtain sufficient serial graphs in 6 per cent or by the fact that tracings were not repeated or could not be in 12 per cent.

5. This study should emphasize the necessity of treating a patient on the basis of clinical evidence until such time as a corroborative electrocardiogram is obtained, and that in the interval we should not permit a nonspecific or normal tracing to dictate our therapy.

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Books Received

New books received are acknowledged each month. As space permits, books of principal interest to our readers will be reviewed more extensively. Reviews will be found in this issue starting on page A-130 and additional listings on pages 348, 435 and A-138.

Natural Childbirth. By H. B. Atlee, M.D., Head, Department of Obstetrics and Gynecology, Dalhousie University, Halifax, Nova Scotia. A monograph in the American Lectures in Gynecology and Obstetrics, edited by E. C. Hamblen, M.D., Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine, Durham, North Carolina. 79 pages. 1956, Charles C Thomas, Springfield, Illinois. $2.75.

The Clinical Psychologist. By William A. Hunt, Ph.D., Professor of Psychology and Chairman, Department of Psychology, Northwestern University, and Lecturer in Psychology, Department of Neurology and Psychiatry, Northwestern University Medical School, Evanston, Illinois. 206 pages. 1956, Charles C Thomas, Springfield, Illinois. $5.50.

Ulcers of the Legs. By Pedro Piulachs, M.D., Chief Professor Surgeon, Faculty of Medicine, Barcelona, Spain. 574 pages with 303 figures. 1956, Charles C Thomas, Springfield, Illinois. $15.50.

Angiocardiographic Interpretation in Congenital Heart Disease. By Herbert L. Abrams, M.D., Assistant Professor of Radiology, and Henry S. Kaplan, M.D., Professor of Radiology, Stanford University School of Medicine, San Francisco. 233 pages, illustrated. 1956, Charles C Thomas, Springfield, Illinois. $11.75.

Clinical Selections in Dermatology and Mycology. By Frederick Rehm Schmidt, M.D., Associate Professor of Dermatology, Northwestern University Medical School, Chicago (with contributions by 36 specialists from various countries). 505 pages. 1956, Charles C Thomas, Springfield, Illinois. $10.50.

Textbook of Urology. By Victor F. Marshall, M.D., Associate Professor of Clinical Surgery (Urology), Cornell University Medical College, New York. 268 pages, illustrated. 1956, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. $5.50.

The Premarital Consultation; A Manual for Physicians. By Abraham Stone, M.D., Associate Clinical Professor of Preventive Medicine, New York University College of Medicine; Director, Margaret Sanger Research Bureau, and Lena Levine, M.D., Associate Medical Director, Margaret Sanger Research Bureau, New York. 90 pages, illustrated. 1956, Grune & Stratton, Inc., New York and London. $3.00.

A Practical Guide to the Management of Intermittent Claudication and the Prevention of Gangrene

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THE diagnosis of intermittent claudication is acceptable when physical exertion produces pain or paresthesia in the foot, calf or thigh, promptly relieved by cessation of the activity without change of position of the affected part. It never occurs in the legs as a result of standing, reclining or sitting and it has no relationship to the muscle cramps which patients have in bed. It is now generally accepted that intermittent claudication results from muscular ischemia secondary to arterial occlusive disease when blood supply is adequate for resting muscle but inadequate for actively contracting muscle. In the vast majority of patients with claudication the pedal pulses are absent. So constant is this finding that if a patient complains of pain in the leg and the arterial pulses are full and bounding, the symptom almost certainly is not due to arterial insufficiency.

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Critique of Current Therapy for Intermittent Claudication

To provide effective therapy, the physician must be cognizant of certain facts about the syndrome and of the patient's reaction to his disability. Spontaneous improvement in intermittent claudication shortly after its onset is observed frequently. Significant variations in exercise tolerance occur naturally in the course of the disease. After occlusion of a major artery in an extremity, one may expect an increase in collateral circulation during the first year; this increase may continue for two or three years, independent of therapy.

The initial distress of the patient with intermittent claudication is often out of all proportion to the actual disability. This discrepancy

is due, in some cases, to the fact that the syndrome represents the first serious physical impairment encountered in a vigorous, active life and one that is envisaged as becoming inexorably more confining as time passes. Other persons interpret "hardening" of the leg arteries to mean the inevitable spread of vascular disease to other vital organs. Finally, there are those who equate intermittent claudication with gangrene and amputation. The physician who fully appreciates such fears is in an excellent position to help these patients.

In practice, the disability in most cases of intermittent claudication is not profound; only a small percentage of patients have to change their employment because of a limited exercise tolerance. Furthermore, intermittent claudication does not have the same prognostic relation to gangrene and amputation that angina pectoris has to death from myocardial infarction, cardiac arrhythmia or congestive heart-failure.

In this clinical setting, therapeutic attempts to alleviate claudication should be essentially devoid of risk.

Today there is no single effective measure for the treatment of intermittent claudication that has gained wide acceptance. Much interest exists in the therapeutic value of interrupting sympathetic tone either medically or surgically. Although there is little evidence that the arteriolar vessels are in spasm in intermittent claudication, it has been assumed that dilatation of the arteriolar and postarteriolar bed will improve the nutrition of ischemic tissue. Unfortunately, methods such as measurement of skin temperature and limb volume changes do not record effective capillary blood flow but rather increments in the total amount of blood or the rate at which blood passes through a portion of the extremity. There is evidence that sympathetic denervation produces a relaxation of the direct arteriovenous communications as well as of the arteriole-metarteriole-capillary network. Whether it is possible, therefore, to improve capillary blood flow by removing normal tone is not at all clear. The observation that interruption of sympathetic activity may increase skin temperatures does not necessarily imply a similar vasodilatation in deep structures. The reverse has, in fact, been claimed. Some observers believe that interruption of normal sympathetic tone (even without producing systemic hypotension) occasionally may aggravate ischemia. Secondary arterial and venous thrombosis has been implicated; the mechanism whereby such a catastrophe could occur might be extensive diversion of blood from ischemic tissue through dilated arteriovenous sluices.

Systemically administered vasodilators may cause generalized vasodilatation with a decreased blood flow to the legs. It is clear that there is a relatively greater "resistance" to the interruption of sympathetic tone in the lower as compared with the upper extremity. This resistance may require the use of relatively large doses of sympatholytic agents with resulting hypotension and tachycardia. Among patients with coronary artery disease such disturbances in hemodynamics may precipitate myocardial ischemia and even necrosis. In this regard it is essential to recall the high incidence of coronary artery disease among patients past 50 years of age as well as the fact that many patients may have coronary artery obstruction without clinical manifestations. In the great majority of patients with intermittent claudication, therefore, the systemic use of potent vasodilator drugs probably is contraindicated.

There have been several reports of the value of intra-arterial vasodilators in the management of intermittent claudication. This route of administration, it has been claimed, will minimize the systemic effects of the drugs. Recently, however, the intra-arterial injection of PRISCOLINE® has also been reported to cause myocardial infarction. Intra-arterial therapy requiring repeated arterial puncture invites, of course, the risk of thrombosis in sclerotic arteries. The value of such treatment in patients with advanced obliterative disease remains to be established.

Surgical sympathetic denervation has been claimed to produce a "local" vasodilatation and relief from the pain of claudication. Yet, lumbar sympathectomy causes a response not only in the ischemic area but throughout the entire extremity. As mentioned before, there

is inadequate evidence that effective nutritional blood flow is increased by this procedure. Finally, experimental and clinical data indicate that in a large majority of cases, return of sympathetic tone occurs within months of the operative procedure, even though the foot may remain warm. These observations tend to invalidate the claim that sympathectomy has any "prophylactic" value in preventing intermittent claudication.

For patients with intermittent claudication and arteriographic evidence of a segmental occlusion in the femoral artery, resection of the occluded zone and its replacement with a venous or an arterial graft has been recommended. Such a procedure, it has been argued with justification, would deliver blood to the tibial arteries at a more effective pressure. This potential advantage, however, must be balanced against the limited disability produced by the claudication and the multiple risks of the operative procedure itself. Segmental arterial resection for intermittent claudication remains an experimental procedure; it is our opinion that the underlying pathologic disturbance and the clinical course of the disability will ultimately cause this therapeutic approach to be discarded.

Tenotomy of the Achilles tendon is another procedure recommended for the relief of intermittent claudication. It is well established that uncomplicated claudication invariably can be relieved by slowing the rate at which the patient walks; tenotomy effectively achieves such a reduction in speed. However, it is usually possible to induce patients to walk more slowly without resorting to psychosurgery.

Despite the apparent therapeutic nihilism expressed in the preceding paragraphs, a detailed, concrete and positive program can be offered the patient suffering from intermittent claudication. On the basis of the pathologic physiology and the emotional responses referred to earlier, every physician can treat these patients effectively without intricate diagnostic or therapeutic technics. The following description summarizes the approach currently used in the treatment of intermittent claudication at the Beth Israel Hospital in Boston.

Practical Management of Intermittent Claudication

1. Establishing the diagnosis—Many patients are referred with an incorrect diagnosis. It is important to remember that the diagnosis of claudication is made entirely by the history. As the diagnosis carries considerable significance to the patient, it should not be accepted lightly. Fortunately, claudication is one of the most specific of symptoms. It is brought on only by continuous exercise and is relieved promptly by discontinuing the exercise without changing the position of the affected part. Furthermore, it is most unusual to be unable to demonstrate some impairment of the peripheral pulsations in these patients. Attention to these simple details will eliminate errors in diagnosis.

The oscillometer remains overrated as an aid in estimating the degree of arterial insufficiency or the severity of intermittent claudication. The limitations of the instrument are emphasized by situations in which the arterial circulation is excellent and yet the oscillometric excursion is small. Occasionally, careful palpation reveals pulsations which are not recorded by the oscillometer.

In the past, undue significance has been attached to the presence of calcification in the walls of atherosclerotic vessels. The clinical effects of atherosclerosis are not dependent so much on "hardening" of the vessels as on narrowing or obliteration of the lumen. Recent studies have clearly demonstrated the absence of any correlation between calcification and occlusion in patients in whom the clinical picture of atherosclerosis and gangrene was sufficiently severe to necessitate amputation[1] (figure 1). These observations indicate that the taking of a roentgenogram merely to determine whether or not arterial calcification is present does not contribute materially to the diagnosis of intermittent claudication.

2. Determining the ancillary factors—Having established that intermittent claudication is present, one must next search for ancillary factors important in increasing the disparity between blood supply and demand. The most common of these are congestive heart-failure

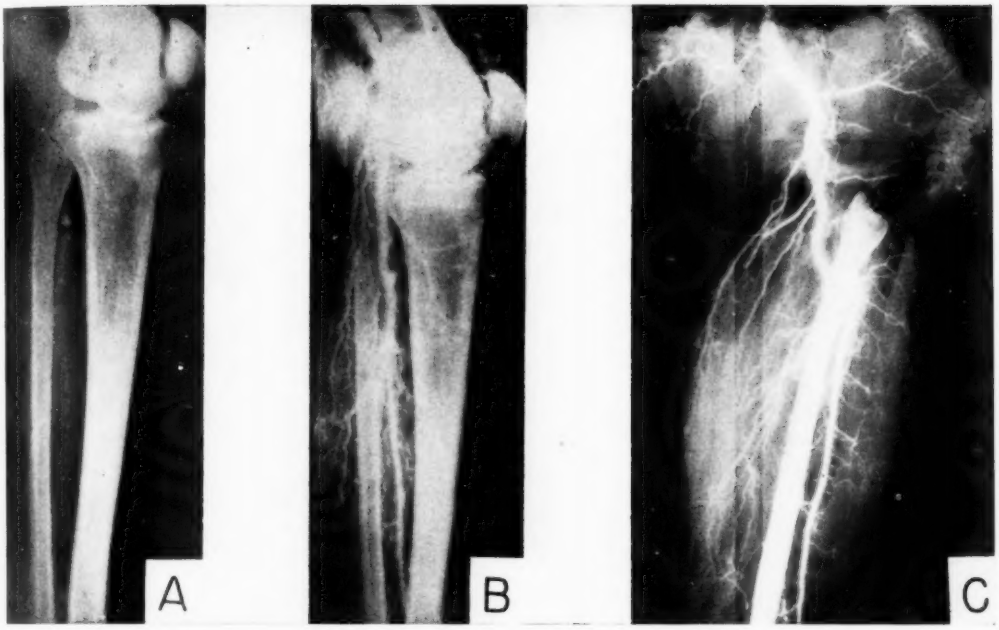

FIGURE 1. Roentgenograms of amputated leg showing inverse relation between arterial calcification and occlusion.

A. Lateral roentgenogram prior to arterial injection of radiopaque medium. Visible calcification of entire popliteal and anterior tibial arteries and upper fourth of posterior tibial artery.

B. Lateral roentgenogram after injection. Calcified popliteal, anterior tibial and upper fourth of posterior tibial arteries patent. Occlusion of remainder of noncalcified posterior tibial and all of peroneal arteries.

C. Roentgenogram of leg after it has been "unrolled" so that major vessels lie in one plane. Sites of patency and occlusion are shown more clearly than in B.

and anemia; their correction will significantly decrease the extent of arterial insufficiency in the extremity. With surprising frequency, patients with claudication are more seriously disabled by an unrecognized coexisting disability than by their arterial insufficiency. Night cramps abolished by quinine or PYRIBENZAMINE®, flatfoot corrected by arch supports, the postphlebitic syndrome ameliorated by elastic bandages, or chronic gouty arthritis relieved by uricosuric agents may so improve a patient's walking tolerance that the discomfort from the claudication alone is no longer disabling. If some such ancillary disability is diligently searched for in each patient with claudication, the therapeutic yield will be very gratifying.

A positive program also requires a re-evaluation of the medical profession's attitude concerning smoking. The continued use of tobacco by patients with intermittent claudication is still strongly interdicted by many authorities. The fact that tobacco smoking increases the tone of peripheral vessels is adequate justification for urging all patients with acute arterial insufficiency to stop smoking, at least until the imbalance between obstruction and collateral flow has been improved. It is equally justifiable, on the basis of a substantial body of clinical data, to urge all patients with thromboangiitis obliterans to abstain from tobacco. However, for the large group of ambulatory patients with intermittent claudication from atherosclerosis, the need for such

restriction is not so clear. There is no evidence that tobacco, any more than mildly cold weather, adversely affects the course of the disease. Some investigators have been unable to demonstrate any deleterious effects of tobacco on intermittent claudication due to atherosclerosis. Others have permitted patients to smoke a few cigarettes daily without apparent harm. For many of these individuals, tobacco smoking is a well-entrenched habit, and abstinence may be neither necessary from the organic point of view nor desirable for emotional reasons. Although there are cogent nonvascular reasons for discouraging the use of cigarettes, we no longer insist that patients with stable intermittent claudication secondary to atherosclerosis discontinue tobacco as part of the therapy of their peripheral arterial insufficiency.

3. Assessing the disability—Having established the accuracy of the diagnosis and satisfied oneself that all potentially related disorders have been adequately explored and treated, one comes to the third aspect of management, evaluating the disability. At the outset, one must recognize and deal with the psychologic hazards induced by the diagnosis itself. The significance of the disability to the patient is perhaps the most important limitation imposed by the syndrome. Failure to meet this problem squarely, particularly since a quick cure cannot be effected by drugs or surgery, will result in failure of treatment or loss of the patient, or both. The fact that claudication will usually improve or at least remain stationary and not bar him from gainful employment should be clearly explained to the patient. This assurance will be reinforced when the patient observes that if he reduces his speed he can walk farther before experiencing pain. Many patients have developed a pattern of rapid walking and it may be necessary to re-educate them to walk more slowly.

4. Walking program—Almost routinely, a walking program is recommended to each patient. He is urged to walk to pain tolerance at least four times daily. To present such therapy to a patient effectively, the physician must be convinced that the virtues of the plan are real. Walking to pain tolerance provides the most physiologic stimulus yet devised for the development of a collateral circulation in those areas where it is most needed, namely, the ischemic zone. Second, it offers the patient a specific program which is simple and completely safe. Gangrene of a toe cannot be induced by excessive walking, per se. Third, walking to pain tolerance has a most salutary effect on that large group of patients who, prior to seeing a physician, voluntarily had limited their activity to avoid pain. Invariably, these patients had assumed that the pain itself was in some way harmful or undesirable. Finally, the walking routine promptly acquaints the patient with improvement as it develops; a blood count or an oscillometric reading is not needed to convince him or to suggest to him that he is better.

Prophylaxis of Gangrene

The following section is concerned with a different group of patients in whom impending gangrene is the main problem. Current conservative management has been largely responsible for the marked decrease in amputations, the successful use of more limited operative procedures, and the relatively advanced age at which major amputations are now necessary among patients with occlusive arterial disease. All therapeutic measures aimed at averting or limiting gangrene have as their goal a decrease in the disparity between the supply and demand for blood by ischemic tissue. Any therapeutic procedure diverging from this aim may precipitate necrosis.

The prominence of diabetes among patients with peripheral arteriosclerosis and gangrene is impressive. If glucose tolerance curves are obtained in all cases of arterial occlusive disease and gangrene, the incidence of diabetes becomes even greater.[2] The infrequency with which gangrene necessitating major amputation has developed in patients with normal glucose tolerance curves has been so striking among our cases of peripheral arterial obstruction that we have found this simple test to be of considerable value in predicting the clinical course of arterial insufficiency. The severity of the diabetic state is not related

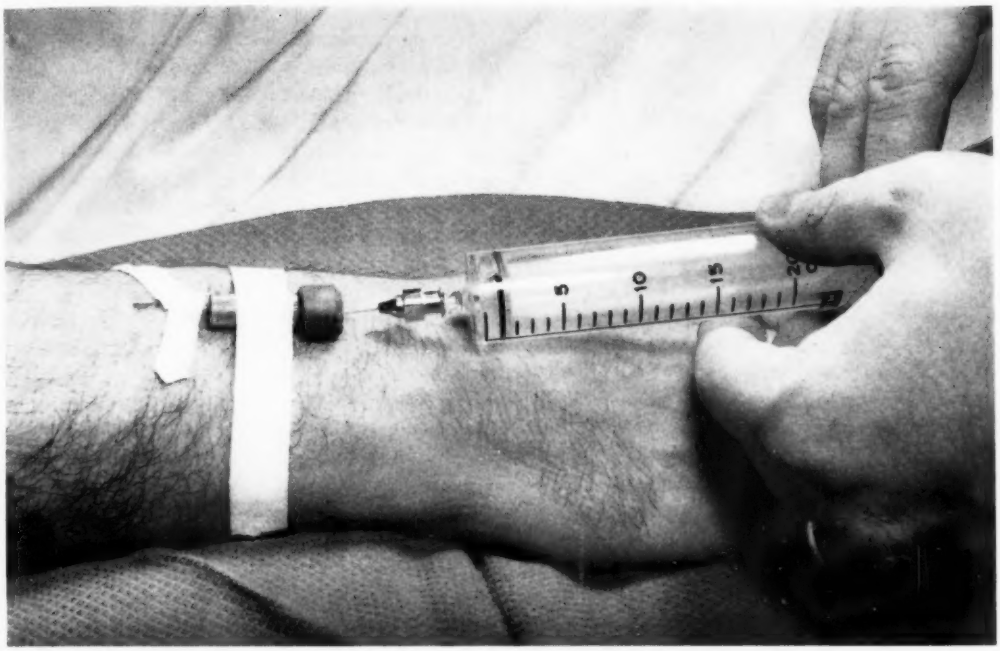

FIGURE 2. Photograph of intravenous injection of heparin through rubber-capped Tuohy-Borst adapter attached to indwelling polyethylene catheter inserted into superficial forearm vein.

to the development of gangrene; in many patients the metabolic defect can be recognized only after examination of the blood sugar. Diabetes, therefore, should be suspected in every patient with peripheral atherosclerosis.

A fresh embolic or thrombotic arterial occlusion may precipitate gangrene. Factors such as hypotension and polycythemia which favor the development of intravascular thrombosis, therefore, require prompt and effective correction. In every patient in whom a fresh arterial occlusion led to gangrene at the Beth Israel Hospital during the past five years, extensive propagation of the clot was found. Since one cannot predict in which case extension of a fresh occlusion will occur, we have considered all patients with fresh arterial occlusion as medical emergencies and have treated them promptly with anticoagulants.

At present an ideal anticoagulant is not available. There is some experimental and clinical evidence to indicate that substances such as DICUMAROL® which depress prothrombin conversion may not provide optimal anticoagulant activity. At present we consider heparin the drug of choice in the short-term treatment of acute arterial occlusion. Recently a new method has been described for the intermittent intravenous administration of heparin without repeated venipunctures.[3] The technic is based on the use of inlying polyethylene catheters attached to rubber-capped Tuohy-Borst adapters (figure 2). Catheters have remained in veins for as long as six weeks without the development of ascending thrombophlebitis or systemic reactions. In some patients there may be a slight localized reaction to the catheter after several days; the polyethylene tubing is then removed and a new catheter inserted at another site. The method has been used successfully in the prophylaxis and treatment of thrombo-embolism in patients with a variety of underlying pathologic states.

FIGURE 3. Bilateral low thigh amputation in 60 year old diabetic man with healed myocardial infarction and congestive heart-failure. There has been excellent functional result for one year.

In approximately half of the cases in which gangrene develops, a history is obtained of avoidable trauma, unnecessary minor surgery of the toes or the injudicious use of various local applications. Experience with ischemic extremities has demonstrated repeatedly that patients with extensive occlusive disease may be protected from gangrene by diligent care of the feet. Conversely, in the presence of proved minimal occlusive disease a severe, neglected insult to the leg may result in extensive gangrene even in the presence of pedal pulsations. It is this knowledge which fully justifies the effort involved in acquainting each patient with the minutiae of good foot care. This is particularly important among patients with diabetic neuropathy or impaired vision.

The following type of instructions may be profitably given to each patient with intermittent claudication.

1. Avoid temperature extremes—Do not expose the feet to cold water or low temperatures that may produce frostbite. Do not bathe feet in hot water and avoid exposure of the legs to hot water bottles, electric pads, sun or ultraviolet light. The complaint of cold feet at night frequently can be relieved with warm socks and blankets rather than by the direct application of heat.

2. Avoid mechanical trauma—Toenails must be trimmed carefully to avoid nicking the skin and cut straight across to prevent ingrowth of the nail. Rough nail edges or nail splitting can be avoided by soaking the toes in warm (not hot) water prior to cutting. If vision is poor or if for any other reason difficulty is encountered in cutting the nails, they should be trimmed by a member of the family or a qualified chiropodist. Patients are advised that it is extravagant to save money on shoes. Shoes must fit well, be made of relatively soft leather, and be broken in slowly to avoid blisters. Coarse socks are undesirable because they tend to wrinkle. Corns and calluses usually can be traced to inadequate shoes or poor metatarsal arches. If these defects are corrected, the thickened layers of skin will soften gradually and can be gently removed. If chiropody is necessary, the chiropodist should be informed of the vascular problem. The patient is instructed never to go about the house without slippers or walk barefoot to the beach, lest injury be incurred from some unsuspected object on the floor or ground. Crowded places where the feet may be injured also demand special care on the part of the patient.

3. Local hygiene—The feet must be kept clean by frequent bathing (at least every other day). The skin must be thoroughly dried with a towel after bathing and then powdered with plain, nonmedicated talc. If feet perspire freely, a change of socks preceded by powdering of the feet should be carried out twice daily. In addition to cleanliness and dryness, it is imperative that the skin be kept soft and pli-

able so that it remains free of cracks which can lead to gangrene. The application of a very thin layer of lanolin to the feet nightly is very effective in this regard. The feet may be covered with cotton or wool socks to avoid soiling the bed sheets. Excess lanolin should always be removed with cotton before applying the sock. Prevention of fungous infection can be achieved by keeping the feet dry and avoiding sources of contamination such as public baths, showers and swimming pools. Finally, no medicine or chemical should be applied to the foot unless prescribed by a physician.

In general, bland powders, lanolin and certain nonsensitizing antibiotic ointments (for the treatment of local infections on advice of a physician) are the only substances that may need to be applied to the skin of the ischemic extremity.

4. Injury—Minor injuries, particularly those involving a break in the skin, justify a call to a physician. When in doubt, bed rest and exposure of the foot to room temperature without the weight of bedclothes is the safest treatment until the doctor arrives.

Gangrene rarely appears *de novo* even in the limb with extensive old arterial obstruction. It usually develops because of the additional burden brought on by fresh arterial occlusion, diabetes, congestive heart-failure, anemia, trauma or infection. At present, therapeutic measures are readily available to meet these major threats to the viability of the ischemic limb. Today, short of a cure for atherosclerosis, prophylaxis remains the real key to therapy. By insuring proper care of his feet, the patient and his physician rather than the extent of the occlusive disease per se will largely determine the incidence of gangrene and amputation.

Rehabilitation

The catastrophic sequelae of amputation, both physical and emotional, can be overcome effectively by a sensitive and flexible yet dynamic approach which has as its basic goal the return of the vascular amputee to an ambulatory status. Although such aims are readily accepted by physicians for young patients with post-traumatic amputations, there has remained among many members of the medical profession a reluctance to embark on such "ambitious" programs in cases of elderly patients who are frequently handicapped by additional disabilities, such as pulmonary insufficiency, congestive heart-failure, hemiplegia and arthritis. The salvage rate among these elderly diabetic amputees is surprisingly high. We have been particularly impressed with the simplicity of achieving a good functional result in many of these patients. The key to such success is early ambulation. Close liaison with a competent limb-maker has resulted in an initial fitting on the fifth or sixth postoperative day when the dressing is first removed, and the availability of the prosthesis within two weeks of the amputation. Thus, guidance and support of the patient in adjusting to the limb and in gait training, which at first seems overwhelming to the patient, are handled in the hospital setting. Occasionally the successful use of a prosthesis is achieved only through the combined and sustained efforts of the departments of physical medicine, surgery, medicine, psychiatry and social service. We are convinced that this type of integrated approach is justified by the striking results that are frequently achieved (figure 3).

Summary

The diagnosis and therapy of intermittent claudication are critically reviewed. A detailed, concrete and positive program is described whereby every physician can effectively treat patients with intermittent claudication without recourse to intricate diagnostic or therapeutic technics. Therapeutic measures for preventing gangrene are discussed and instructions for good foot care are presented in detail. A program for the ambulation of the vascular amputee is outlined.

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Experience With Fibrinogenopenia

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DURING the eight years between 1946 and 1954, among approximately 8000 consecutive obstetric deliveries at the Colorado General Hospital, fibrinogenopenia has occurred in only three cases. The disease does not represent a great problem in any one hospital, but its community incidence is of profound importance because of the number of maternal deaths which may accumulate from the severe forms.

Two of the three cases of fibrinogenopenia were associated with abruptio placentae. The third patient demonstrated the acquired clotting defect as a complication of maternal sensitization to the Rh factor while carrying an erythroblastotic fetus which had died in utero.

In addition to these three cases, we saw four other patients with fibrinogenopenia in consultation. In all four cases the deficiency was associated with abruptio placentae.

The clotting defect seemed to be corrected in four of the cases of fibrinogenopenia and abruptio placentae by the substitution of human fibrinogen, but two of the patients failed to survive because of other severe complications of the disease.

Our first case of afibrinogenemia was that of a patient seen in 1947, and we were at a loss to know how to cope with the problem.

Case 1—This patient was in the hospital under treatment for mild preeclampsia of some weeks' duration. She was given intravenous human salt-free albumin as part of her treatment. While receiving the albumin, she experienced a severe chill. The albumin was discontinued. Shortly thereafter the patient had a generalized convulsion and started to bleed from the gums, nose, rectum and vagina, and signs of severe abruptio placentae appeared. Samples of her venous blood failed to clot. This crisis occurred in 1947, before fibrinogenopenia was understood and before human fibrinogen became available for therapeutic use. The patient never regained consciousness and died within 15 hours. Pathologic examination revealed lesions in the kidney, brain and

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liver which were compatible with eclampsia. Gross hemorrhage was present throughout the respiratory, genital and digestive tracts. A massive retroplacental extrusion of blood was found within the uterus. The dead fetus was undelivered.

Reports then began to appear in the literature to bring this serious but unusual complication to our attention. De Lee,[1] Kellogg[2] and others had spoken of the syndrome, but most clinicians either had never encountered such a problem or had presumed that uterine atony was the cause of hemorrhage and death. There was the belief that a Couvelaire uterus and uterine atony were the essential causes of postpartum hemorrhage. Formerly, hysterectomy was advised and performed. Severe grades of uterine bleeding were not cured by hysterectomy, and patients died because of generalized purpura. It is now believed that the specific problem was afibrinogenemia. It is not known whether there is a gradual depletion of fibrinogen before the bleeding tendency appears or whether there is a sudden depletion of this factor through massive intravascular deposition of existing fibrinogen in the form of fibrin.

In 1951 we obtained from Dr. Duncan E. Reid and Dr. Louis K. Diamond of Harvard a supply of human fibrinogen. This had been prepared under the auspices of the American Red Cross and was sent to us for emergency trial use in obstetrics with the provision that we report our clinical results to Drs. Diamond and Reid. We were warned of the possible infectious hepatitis that might appear later as a result of fibrinogen administration.

Later, the Division of Laboratories, Michigan Department of Health, Lansing, Michigan, through H. B. Anderson and K. B. McCall, provided us with human fibrinogen for clinical trial. The Michigan program was also sponsored by the American Red Cross.

We have been called on five times in the past four years to administer fibrinogen, in four instances for abruptio placentae and once for a fibrinogen depletion associated with intra-uterine death of an Rh positive fetus in an Rh negative mother. A brief report on the latter patient follows.

Case 2—This patient was Rh negative and had a high Rh antibody titer. Intra-uterine fetal death occurred five weeks before the patient's admission to the hospital. On admission she exhibited edema, albuminuria and hypertension. Ecchymotic spots appeared on the forearm when a tourniquet was left on the arm for several minutes. A fresh blood sample clotted poorly after 15 minutes and incubation of the clot for one hour at body temperature caused it to disintegrate. She was given 6 gm. of human fibrinogen intravenously and a stable clot resulted. Since the patient previously had had a cesarean section it was decided to perform a hysterotomy to remove the dead fetus and placenta. One hour after the operation, shock developed and the patient died. The pathologic tissue examination showed massive intravascular deposition of fibrin.

Comment—It is felt that the cesarean section and the trauma associated with it provided the final insult to a very disturbed physiology. Probably the replacement of fibrinogen was inadequate. Blood levels of fibrinogen should have been studied in relation to both diagnosis and replacement therapy. Subsequent experience by ourselves and others has shown that this condition must always be anticipated if a fetus dies in utero and is not delivered after five or six weeks. The patient's blood should be tested repeatedly to determine clotting ability, and plasma fibrinogen levels should be obtained if intra-uterine fetal death has occurred. There have been no reports of maternal fibrinogenopenia occurring prior to the fifth week after an intra-uterine fetal death.

Case 3—This patient had severe preeclampsia at term and came to the hospital with the additional finding of severe abruptio placentae. The membranes were artificially ruptured. The patient bled freely from venous puncture wounds, and afibrinogenemia was demonstrated. She was given 4 gm. of human fibrinogen intravenously. PITOCIN® was administered in a venous infusion of distilled water to stimulate labor. The clotting defect was corrected. The patient delivered a stillborn infant vaginally 13 hours after rupture of the membranes and recovered satisfactorily.

Comment—The current opinion is that such

a patient should be delivered abdominally if vaginal delivery does not occur rather promptly after correction of the afibrinogenemia and rupture of the membranes.

Case 4—This patient represented the one maternal death and the second case of afibrinogenemia in our series of 70 patients with abruptio placentae seen at the Colorado General Hospital in the eight years covered by this report. The severe detachment of the placenta was a complication of preeclampsia. Complete separation of the placenta was associated with fetal death, profound maternal shock and demonstrable fibrinogenopenia. Human fibrinogen, 6 gm., and several blood transfusions corrected the fibrin deficiency. The membranes were ruptured artificially and vaginal delivery occurred eight hours later. The patient's clotting deficiency was corrected, but she died three months later of acute adrenal insufficiency, secondary to necrosis of the pituitary gland. It was felt that the latter condition, which was found at autopsy, was the result of obstetric shock.

Comment—This patient died of complications of the abruptio placentae syndrome which were unrecognized before death. The fibrinogenopenia, however, was corrected during the period of emergency treatment.

Case 5—This patient had toxemia of pregnancy, severe abruptio placentae, fibrinogenopenia and twin stillborn infants. Her clotting difficulty was corrected by administering 4.5 gm. of fibrinogen. Cesarean section was performed one and one-half hours after the fibrinogen was administered, and when artificial rupture of the membranes and Pitocin failed to effect delivery. Artificial rupture of the membranes was performed two hours before cesarean section. The patient recovered.

Comment—The fibrinogen deficiency was recognized and treated promptly. The membranes were ruptured to relieve intra-uterine pressure and to induce labor. Labor did not start promptly even with Pitocin stimulation. Abdominal hysterectomy was elected, the fibrinolytic process was arrested, and the patient recovered.

Case 6—This patient had a normal pregnancy until hypertension, albuminuria, severe abruptio placentae and fibrinogenopenia developed suddenly during the course of labor. Obstetric shock occurred which was out of proportion to the amount of blood lost. Immediate blood transfusions and 6 gm. of fibrinogen were administered. The bleeding tendency seemed controlled and the patient improved. Three hours after delivery a second episode of obstetric shock appeared. The patient bled from the vagina and again the blood showed no tendency to clot. Fibrinogen was again administered (3 gm.), but the patient died one-half hour later, four hours after delivery.

Comment—Analysis of this death in light of present experience suggests that it may have been preventable. The first symptoms of abruptio placentae occurred 12 hours before death. Delivery was accomplished after seven hours of symptoms, and although the abruptio placentae syndrome was recognized immediately the fibrinolytic syndrome was not recognized until after delivery. According to our present knowledge of this disease process it is imperative to recognize the afibrinogenemia early, treat it, and then empty the uterus by cesarean section soon thereafter if labor does not progress quite rapidly.

Case 7—This patient had an accidental placental separation characterized by continuous abdominal pain, vaginal bleeding and sudden cessation of fetal movements. Six hours later she arrived at the hospital, with moderate shock, preeclampsia and abruptio placentae. A blood sample failed to clot on standing for several hours. Shortly after admission to the hospital the patient delivered a term-size stillborn infant vaginally. A 1000 cc. postpartum hemorrhage occurred. The patient was given 3 units of whole blood, the clotting defect was corrected soon after delivery, and she made a satisfactory recovery.

Comment—This patient had a severe abruptio placentae syndrome with fibrinogenopenia, and despite the presence of the symptoms of separation for six hours, she recovered. This tends to illustrate that the disease process may not always be fatal although untreated with fibrinogen.

To summarize these seven cases, there were

six patients with abruptio placentae and one patient carrying a dead fetus in utero who demonstrated fibrinogenopenia. Four of the seven died. Three had adequate fibrinogen replacement but died of complications of the disease after the clotting defect was corrected.

Anderson, McCall and Hertell,[3] through collected experiences reported to them at the Michigan State Health Department, reported 131 patients treated with fibrinogen with 22 deaths. Almost half the patients treated were diagnosed as having abruptio placentae, and almost two-thirds had conditions associated with pregnancy. Of the 64 cases of abruptio placentae reported to them in which the patients were treated with fibrinogen, 60 responded satisfactorily. Only one of these patients died from hemorrhage that failed to respond to the administration of fibrinogen.

Amniotic fluid embolus has been reported as being capable of producing sudden afibrinogenemia.[4] While we have encountered three patients who were thought to have had amniotic fluid emboli, we have not seen an instance of afibrinogenemia occurring as a result of a recognized amniotic fluid embolus.

Any intra-uterine fetal death conceivably might lead to afibrinogenemia if the dead fetus remains in the uterus for a long period. In our series, afibrinogenemia occurred in a case of intra-uterine death of an erythroblastotic infant five weeks after the fetal death. When an intra-uterine fetal death has existed for as long as 35 to 40 days the patient's blood should be checked for fibrinogen depletion.

Cutter Laboratories recently have produced a purified human fibrinogen that is now available for treatment of hypofibrinogenemia. It is prepared in 1 gm. packages complete with diluent and administration set. The product is still quite expensive and appears under the name Parenogen. It is safe and effective, according to our present knowledge.

It is difficult to give a set plan of advice for the management of the serious obstetric complication of hypofibrinogenopenia. When the condition appears, it is necessary to make the diagnosis as early as possible. In addition to abruptio placentae, amniotic fluid embolus and fetal death in utero, varying degrees of hypofibrinogenemia have been reported in association with abortion,[5] retained placenta[6] and eclampsia.[7]

The plasma fibrinogen level in a normal pregnant patient at term is about 400 mg. per 100 ml.[8] When plasma fibrinogen levels are found materially below 400 mg., and particularly when they reach 100 mg. or lower, a hemorrhagic diathesis from fibrinogenopenia may be anticipated.[9] Our opinion is that when one is dealing with a potential candidate for hypofibrinogenemia, repeated plasma determinations for fibrinogen should be performed.

Clotting deficiency or hypofibrinogenemia should be corrected by administering 2 to 6 gm. of human fibrinogen. Whole blood must be used in sufficient quantities to replace blood loss and combat shock if active bleeding has occurred. When the patient's condition is satisfactory, the uterus should be emptied by the most atraumatic and the most expedient method. For some patients, cesarean section may be the best treatment; for others, rupture of the membranes and Pitocin stimulation may be most beneficial. Until the uterus is emptied, the threat of afibrinogenopenia exists, and the more extensive the process of placental separation the greater the amount of thromboplastin released to the general circulation. Artificial rupture of the membranes may reduce the amount of thromboplastin being liberated from the placental site and hasten the process of labor.

Summary

Personal experience with fibrinogenopenia over an eight year period is presented. Seven cases of fibrinogenopenia are reported and discussed. The causes of afibrinogenopenia are reviewed.

Conclusions

1. In all cases of moderate to severe abruptio placentae or intra-uterine fetal death of over one month's duration, the patient's blood should be studied for fibrinogen deficiency.

2. Fibrinogen deficit should be corrected by administering intravenous human fibrinogen in quantities sufficient to bring the fibrinogen levels to normal.

3. Delivery of the obstetric patient with the fibrinolytic syndrome should occur as soon as the fibrinogen can be satisfactorily replaced, and before the condition has an opportunity to recur.

4. The maternal mortality rate from the fibrinolytic syndrome is extremely high and the condition must be recognized early and treated.

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MEETINGS *and Postgraduate Courses*

American College of Surgeons Sectional Meetings, 1957: San Juan, Puerto Rico, January 16-18. Sessions will be held aboard the S. S. Homeric en route and then at The Caribe Hilton Hotel. Local committee chairman is Dr. Jose Noya Benitez, Professor and Chairman, Department of Surgery, School of Medicine, University of Puerto Rico.

New Orleans, February 4-7. Hotels Jung and Roosevelt. Dr. Howard Mahorner, Clinical Professor of Surgery, Louisiana State University School of Medicine, is chairman of the arrangements committee. Nurses are invited to attend.

Seattle, February 28-March 2, The Olympic Hotel. General committee chairman is Dr. Henry N. Harkins, Professor and Executive Officer, University of Washington, School of Medicine.

Washington, D. C., March 18-20. The Sheraton-Park Hotel. Dr. W. Ross Morris, Associate Professor, George Washington University, School of Medicine, is program director.

Toronto, The Royal York, March 25-27. Program planning is under the direction of Dr. Stuart Douglas Gordon, Assistant Professor of Surgery, University of Toronto, Faculty of Medicine.

St. Paul, April 8-10, Hotels Lowry and St. Paul. Dr. Charles E. Rea, Clinical Professor, University of Minnesota Medical School, is general program chairman.

For additional information write to: Dr. H. Prather Saunders, Associate Director, American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

Eighth Postgraduate Assembly in Endocrinology and Metabolism, Houston: October 22-27, 1956, at Texas Medical Center. Assembly is sponsored by The Endocrine Society. For further information write to: Office of the Dean, The University of Texas, Postgraduate School of Medicine, Texas Medical Center, Houston 25, Texas.

First International Congress of Neurological Sciences, Brussels: July 21-29, 1957. First affiliation of all independent International Congresses into a single convention. Organization centralized under direction of Professor P. van Gehuchten and Dr. Ludo van Bogaert, president and secretary-general of the Belgian National Committee for Sixth International Neurological Congress. Scheduled to meet simultaneously are: Sixth International Neurological Congress, Fourth International Congress of Electroencephalography and Clinical Neurophysiology, Third International Congress of Neuropathology, First International Congress of Neurological Surgery, Third Meeting of the International League Against Epilepsy, and Second Symposium Neuroradiologicum. Program information may be obtained from: Dr. Pearce Bailey, Secretary, Committee for the United States, Sixth International Neurological Congress, National Institutes of Health, Bethesda 14, Maryland.

The National Foundation for Infantile Paralysis announces postdoctoral fellowships for full-time study for careers in research or academic medicine, or in the clinical fields of psychiatry, rehabilitation, orthopedics, the management of poliomyelitis and preventive medicine. Partial fellowships are available for qualified veterans to supplement G.I. educational benefits. Applications must be received by March 1, September 1 or December 1 for consideration in May, November or February, respectively. For further information write to: Division of Professional Education, The National Foundation for Infantile Paralysis, 120 Broadway, New York.

University of Texas, Houston: First annual clinical symposium, November 9-10, at the M. D. Anderson Hospital and Tumor Institute. Management of carcinoma of the breast will be the topic. Dr. Melvin A. Casberg, vice-president in charge of medical affairs for the University of Texas, and Dr. Ian Macdonald, associate clinical professor of surgery at U.C.L.A. and president of the California division of the American Cancer Society, will be among the speakers.

The Problems of Ovarian Tumors

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IT is significant that 62 per cent of all ovaries removed in one hospital in a period of four years were found to be normal.[1] Of the ovaries that were removed in various private hospitals in Los Angeles and adjacent cities in one year and preoperatively diagnosed as showing ovarian pathology, only about 27 per cent were found to be pathologic at operation.[2] Reports such as these indicate that major problems confront anyone who attempts to diagnose and treat ovarian neoplasms. The problems can be classified as follows:

1. Problems of diagnosis
   - (a) Problems resulting from the basic physiology of the ovary
   - (b) Problems due to the characteristic silence of ovarian tumors
   - (c) Problems due to the inaccessibility of the ovaries

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2. Problems of therapy
   - (a) Criteria for therapy
   - (b) Therapy in the nonpregnant patient
   - (c) Therapy in the pregnant patient

To solve these problems, examination must be systematic and thorough, and therapy must be prompt, adequate and exacting.

The first problem in diagnosis is due to the basic function of the ovary. In palpating the adnexa, it is of paramount importance to be cognizant of the phase of the patient's menstrual cycle. When the graafian follicle extrudes the ovum, it changes into a corpus luteum which then regresses in a routine, orderly manner. The normal ovulatory cycle has

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been well illustrated in a drawing by Netter.[3] It can be upset by the retention of structures in any stage of development. The result may be a physiologic derangement which at times may cause distinctive symptoms such as those which occur as a result of polycystic ovaries associated with the Stein-Leventhal syndrome. At other times, this physiologic derangement may mimic other pelvic problems such as the persistent corpus luteum cyst syndrome, which first was described by Halban in 1915. This is characterized by a brief period of amenorrhea followed by irregular uterine bleeding, unilateral pelvic pain, and a small, tender, movable adnexal mass. These can be mistaken for the signs and symptoms of an unruptured ectopic pregnancy.

It is no sin to perform a laparotomy as a result of an erroneous diagnosis in a case in which one of these structures persists with or without symptoms. In fact, this surgical procedure sometimes is necessary in order to eliminate the possible presence of a dangerous neoplasm. Gross recognition of these structures is necessary in order to determine whether or not an operation is indicated. If surgery is indicated, it should be conservative.

The second diagnostic problem is the characteristic silence of ovarian tumors. They have been rightfully called the silent, sneaking killers of women. Pain is a rare symptom of ovarian neoplasms, and it occurs only as a result of complications of the neoplasm. It is the result of confined bleeding, scarring of endometriosis, torsion of an ovarian cyst, or active hemorrhage into a cyst or due to rupture of a cyst. In spite of this, the ovary and the closely associated appendix become the target for all pelvic pain. The surgeon who opens the abdomen in a case of acute appendicitis sometimes is disturbed to find that the appendix is not red but barely blushing. When confronted with an ovary containing functional cysts in all stages of development, he finds it difficult to close the abdomen without also removing the ovary, which he believes is partially responsible for the pain. The pinching pains of a bothered conscience are relieved by rationalizing that if one ovary is left the patient will have more than enough ovarian tissue. It would be a different story if the tables were turned, with the surgeon the victim of a possible orchiectomy.

A similar situation exists when the abdomen is opened for the removal of a cyst that was palpated only a week or a few days before the operation. Surprise and shock result when the surgeon discovers that the cyst, which was a functional cyst, is no longer present. The ovary usually is removed because the cyst might, or without doubt will, re-form if the function is normal. The appendix also is removed to eliminate all the possible causes of pain. Needless to say, the pain often is present after the incision has healed, and it then is attributed to adhesions. It should be re-emphasized that pain rarely is an early symptom of a tumor of the ovary.

The first indication of the existence of an ovarian tumor may be its discovery by routine or periodic physical examination. Early diagnosis of an ovarian tumor possibly can be made by careful examination. Endometrial carcinoma, which often is asymptomatic, frequently can be diagnosed by endometrial biopsy or by uterine aspiration and examination of the aspirated material by means of Papanicolaou's method of staining. A diagnosis of carcinoma of the cervix often can be made in the early stage by means of biopsy or by examination of cervical smears by using the staining method of Papanicolaou. It, therefore, is evident that all women should be urged to have a periodic examination.

The diagnostic significance of enlargement of the abdomen in cases of tumor of the ovary is the same as that of cachexia in cases of tuberculosis. Both of these signs occur late in the course of the respective diseases. In cases of tumor of the ovary, one is interested in early diagnosis. At times, a very small tumor will produce sufficient pressure to cause discomfort in the bladder, rectum and legs. A lesion of the ovary can cause subdiaphragmatic or hypogastric discomfort by a reflex mechanism.

Menstruation is rarely affected. Exceptions are the dysmenorrhea of endometriosis, the menorrhagia associated with a granulosa cell tumor, and the hypomenorrhea or amenor-

rhea associated with an arrhenoblastoma.

One of the chief problems in the diagnosis is "visualization," by palpation, of the ovarian mass that is responsible for the symptoms. In this respect, the diagnosis of a tumor of the ovary is more difficult than the diagnosis of a tumor of the breast or of the cervix or fundus of the uterus. Before one undertakes a gynecologic examination, the patient's bladder should be empty and her bowel should be free of all solid material. The patient should be examined with an unlubricated speculum, and bimanual examination should be made by the abdominovaginal and rectovaginal methods. Such bimanual examination is very valuable in the diagnosis of lesions of the ovary.

What other diagnostic aids are available? At times, the suspected presence of an ovarian lesion can be verified by roentgenographic examination. This diagnostic procedure is useful in distinguishing a huge ovarian cyst from ascites. It may reveal that the course of the sigmoid is so altered that it crowns the tumor. This crowning appearance of the sigmoid is not observed in cases of ascites.

The gynecologic examination of an obese woman is a challenge even when the examination is performed bimanually by the abdominovaginal and rectovaginal methods. Culdoscopy may be of assistance in verifying the suspected presence of an ovarian tumor. Our experience with this diagnostic procedure is limited. We are better qualified to use culdotomy, and have employed this procedure successfully. It not only will allow inspection of the lesion but occasionally will permit correction of a pathologic condition.

We cannot agree with physicians who advocate the aspiration of ovarian cysts through the cul-de-sac of Douglas. This is done without direct vision, and one of the fundamental principles of ovarian surgery is to avoid spilling the contents of a cyst.

We have made a study of the clinical records in 508 cases of tumor of the ovary which were observed at the Milwaukee Hospital. Five gynecologists were responsible for the care of the patients in most of these cases. This hospital, which is a private institution, has an accepted residency training program, and is closely affiliated with the Marquette University School of Medicine for the teaching of senior students.

The tumors were benign in 441 cases. In 367 (83 per cent) of these cases, the correct diagnosis was made preoperatively. In 8 of the remaining 74 cases in this group, the tumor was found in the course of an operation which was performed for some other pathologic condition. The erroneous diagnoses were as follows: fibroids in 41 cases, endometriosis in 15 cases, appendicitis in 5 cases, ectopic pregnancy in 4 cases, and adenomyosis in 1 case.

The correct diagnosis was made preoperatively in 45 (67 per cent) of the 67 cases in which the tumors were malignant. In 3 of the remaining 22 cases in this group, no diagnosis was made preoperatively, but the malignant tumor was disclosed by an exploratory laparotomy. The erroneous diagnoses were as follows: fibroids in 14 cases, appendicitis in 2 cases, ectopic pregnancy in 1 case, endometriosis in 1 case, and carcinoma of the fundus in 1 case.

The results of this study emphasize what can be accomplished in a well-controlled hospital in which exacting diagnosis is a necessity owing to resident and student training.

In order to justify the performance of a radical operation, some surgeons maintain that the incidence of ovarian tumors is high in cases in which an operation has been performed on the pelvis. A previous pelvic operation had been performed in only 27 of the cases which we studied. The ovarian tumor was malignant in 11 of these cases and benign in the remaining 16 cases.

Criteria for Therapy

If clinical examination discloses an adnexal mass, how should the clinical findings be interpreted and how should the patient be treated? No one is infallible. One who has not made an error in diagnosis has not treated a patient. A serious error, namely, scheduling the patient for an immediate operation, can be avoided. Early scheduling of an operation is done partly for the benefit of the patient and partly to avoid losing the patient. Except

in the case of a solid tumor, most gynecologists have learned and are teaching that after a pelvic mass is discovered the patient should be observed for six to eight weeks before operation is performed. During this interval, the patient should be examined every two weeks. If the mass persists in spite of the physiologic changes that can be expected to occur during this interval, and if it is 5 cm. or more in diameter, operation should be performed. Although tumors of this size usually are benign, from 5 to 10 per cent of such tumors are found to be malignant. The physician who plays a hunch that such a tumor is not malignant doesn't have a second chance.

We recently had an experience which emphasizes the necessity for this period of observation. A woman who was employed by a group of physicians came to our office for a pelvic examination. After she was told that she did not have any pelvic lesion, she said that she had been examined after an episode of right-sided pain and that she had been told that she had an ovarian cyst and that the cyst should be removed immediately.

It is a certainty that her physician, who was one of her employers, was sincere and honest, since replacement help is difficult to obtain and train. However, he made a serious error, namely, making a diagnosis without sufficient observation.

The patient was told that the cyst that her physician had palpated probably was either a large physiologic cyst or a corpus luteum associated with hemorrhage. She was told that these frequently regress without intervention. She was satisfied with this explanation, and no harm was done.

We want to re-emphasize that the results of a pelvic examination cannot be evaluated intelligently unless the patient's bladder is empty and her bowel is free of solid material at the time of the examination. The importance of this preparation is illustrated by an experience which a resident and I recently had. A patient was sent to the hospital because of acute pain in the lower part of the abdomen and a palpable mass in this region. The diagnosis was a twisted ovarian cyst. A catheter was inserted to prepare the patient for preoperative examination. This relieved the urinary retention, and the mass and the pain disappeared.

Therapy

If treatment is indicated, the following questions must be answered. What type of tumor is present? What is the patient's age? What is her marital status? Is the patient pregnant?

On the basis of the age of the patient, one should try to anticipate the type of tumor that may be present. This should be done in order that the patient may have some idea of the extent of the operation that may be required. It may not be possible to determine this before the operation. Our past experience indicates that the tumors which occur most frequently in women of the child bearing age are functional cysts, endometrial cysts, pseudomucinous cysts, serous cysts and dermoid cysts.

The malignant tendency of a tumor varies according to the type of the tumor. Non-neoplastic, functional tumors do not have any tendency to become malignant, whereas 35 per cent of papillary cystadenomas do have such a tendency. If an ovarian tumor occurs in a woman who is between 30 and 40 years of age, there is a 25 per cent chance that it will be malignant. There is only a 1 per cent chance that an ovarian tumor will develop in a woman who is more than 50 years old and who has been fortunate enough to retain her ovaries. However, if a tumor does develop, there is a 70 per cent chance that it will be malignant.

In cases in which the patients are just below or just above the age of the menopause, the tendency can be toward a more radical type of operation, although, even now, the complete role of the ovary in the maintenance of body stability in the postmenopausal period is not known. Conservatism should be the guiding policy in operating on women in all other age groups. This is especially true in cases in which endometriosis, with its infertility factor, is present. In our limited experience, we have observed an increase of 50 per cent in the fertility rate in cases of endometriosis in

which a conservative operation has been performed. The conservative approach pays dividends in cases in which tumors have a tendency to occur bilaterally, as dermoid cysts do. A word of explanation to the patient and her family often will clarify the fact that this conservative approach is for their immediate benefit and that another operation may be necessary after childbirth.

How should the therapy of a nonpregnant woman be managed? X-ray irradiation never should be used primarily. The primary treatment of choice is surgical. An operation on the ovary never should be performed unless a cervical smear has been examined by means of Papanicolaou's method of staining. In one of every 100 cases in which this diagnostic procedure is used in a physician's office, it will disclose a carcinoma of the cervix. This statement is based on the use of this procedure in the office of one of us (F. J. H.) with the assistance of Dr. George Savage.

The first step of the operative procedure should consist of preliminary dilatation and curettage. Conservative treatment of an ovarian lesion does not necessarily mean that the uterus should be preserved. However, conservative ovarian surgery is usually the goal if the childbearing function is to be preserved. Therefore, when the uterus is preserved, the status of the endometrial cavity must be known. An incomplete operative procedure may remove the lesion of the ovary but permit progression of an undiscovered lesion in the uterus. This is an error which cannot be excused.

After the abdomen has been opened, a quick appraisal will reveal whether the lesion is grossly unilateral or bilateral and whether it is grossly malignant or benign.

If the tumor is unilateral and benign, should the entire ovary be removed? Absolutely not! The affected portion should be removed, but any normal ovarian tissue, regardless of how small it may be, should be retained. This is especially true in cases in which the patients are in the younger age group. It is impossible to determine the fate of the other ovary. A latent lesion which is not discovered at the time of the initial operation suddenly may become active and necessitate removal of the entire ovary.

In a case in which a patient is known to have a tumor that has a tendency to occur bilaterally, conservatism is especially essential. The unaffected ovary should be bisected from the bloodless edge to the hilar area. Complete inspection then is possible. If a seedling tumor is found, it can be removed and the ovary can be repaired without any permanent damage. This procedure is imperative in cases of dermoid cysts, which tend to occur bilaterally in 25 per cent of cases.

Whenever a cyst or a tumor of the ovary is removed, it should be opened at the operating table before the surgeon does anything else except to control hemorrhage. If gross inspection is not sufficient to determine whether or not the tumor is malignant, it should be examined by a pathologist. A frozen section should be made if necessary. If the tumor is found to be malignant, bilateral salpingo-oophorectomy and total hysterectomy should be performed. Treatment short of this is inadequate. If, when the abdomen is opened, gross examination indicates that the tumor is malignant, an attempt should be made to free the masses in the pelvis, and bilateral salpingo-oophorectomy, total hysterectomy and omentectomy should be performed.

At times, a frozen pelvis will be encountered, and the lesion apparently will be inoperable. Biopsy should be performed to determine whether or not the lesion is malignant. Massive and extensive endometriosis can produce a similar appearance. The prognosis is better in cases of endometriosis than it is in cases of malignant tumor. In either case, the abdominal incision should be closed after biopsy has been performed, and roentgen therapy should be used postoperatively. Massive endometriosis always is made operable by this method of treatment. At times, a malignant tumor will respond so that an adequate operation can be performed at a later date. In cases in which extensive metastatic lesions have covered the abdominal peritoneum, colloidal gold has been of some advantage in controlling the development of ascites. Its value in all other respects has been inconclusive.

The problems of the treatment of an ovarian neoplasm are multiplied if the tumor is discovered while the patient is pregnant. Two axiomatic statements can be made regarding the treatment of a tumor that is discovered at this time. (1) If the tumor is solid, it should be removed as soon as possible. (2) If the tumor is discovered late, the pregnancy should be permitted to progress to term, and cesarean section and removal of the tumor should be performed at that time.

What course should be followed if the tumor is cystic and is discovered early in pregnancy? It is fairly well established that if the operation is performed carefully the tumor can be removed any time after the second month of gestation without disruption of the pregnancy.

Although the results of the administration of stilbestrol and progesterone are inconclusive, there seems to be some indication that these drugs may be of some value if they are administered for six or eight weeks after operation.

It must be remembered that the corpus luteum of pregnancy can attain great size and may create a diagnostic problem. When a cystic tumor is discovered in the first trimester of pregnancy, the possible presence of a corpus luteum must be considered. The patient should be examined every two weeks, and, by the fourth month of gestation, the physician may be rewarded by finding that the cyst has disappeared. Spontaneous disappearance of such a cyst is not unusual.

In a case in which a malignant neoplasm of the ovary occurs in a pregnant woman, the method of treatment is the same as it is in a case in which this type of neoplasm occurs in a nonpregnant woman.

It would be a great advantage for all pregnant women if vaginal examination were performed routinely at the seventh month of gestation. This frequently would disclose ovarian tumors obstructing the birth canal, and it would avoid many catastrophes and emergency cesarean sections.

Why not permit labor to occur in the usual manner if an ovarian cyst lies posterior to the uterus but does not cause any obstruction? If labor is allowed to occur in the usual manner and if delivery is made through the vagina, the cyst may be ruptured. If the cyst is carcinomatous, spillage of its contents may result in widespread metastasis; if it is a dermoid cyst, rupture may cause peritonitis.

A consideration of ovarian tumors associated with pregnancy would not be complete without the mention of large theca-lutein cysts. These cysts occur with an intra-uterine hydatid mole, and they are the result of the abnormal pregnancy. They should not be removed, because they will undergo regression and will disappear completely when the uterus is emptied.

Conclusion

Conservatism should be the guiding policy in the treatment of tumors of the ovary. Preservation of a very small portion of an ovary may make the difference between sterility and the ability of a patient to become pregnant.

Will you, when reviewing your surgical year, be confronted by the psychologic, obstetric and gynecologic wrecks that are the result of too enthusiastic and too radical ovarian surgery?

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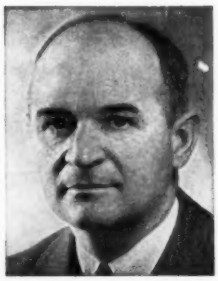
DIAGNOSTIC CLINIC

Surgical Lesions of the Adrenal Gland

WALTMAN WALTERS*

Mayo Clinic, Rochester, Minnesota



WALTMAN WALTERS

DR. James E. Conley of Milwaukee has been kind enough to bring a patient on whom he has operated; we shall discuss that case in relation to medullary tumors of the adrenal. My medical colleague, Dr. Raymond Randall, who is a consultant in the section of metabolic diseases, also is here with me. Dr. Randall's knowledge of the complex chemistry associated with hyperfunctioning adrenocortical tumors will, I know, be of interest to you, because the field is one in which a good deal of specialization is necessary and in which I am not competent to discuss more than the clinical and surgical aspects of these complex steroids in the production of different symptoms and signs.

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Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

I thought the best way to present this material would be to outline briefly what hyperfunctioning tumors of the adrenal will do. You know there are two parts to the adrenal. The first is the cortex, which arises from the same embryologic analogue as do the ovaries and the testes; therefore, when the adrenal cortex, because of tumor formation or hyperplasia and hypertrophy, oversecretes its complex substances, to which Dr. Randall will refer, we have, among other symptoms, the urogenital, including precocious puberty in children, androgenic signs in women and estrogenic signs in men. That is an easy way to remember it. The medullary portion of the adrenal takes its origin from the same analogue that gives rise to the sympathetic nervous system; therefore, when this part of the gland is affected, we have changes associated with stimulation of the sympathetic nervous system, such as hypertension, undue sweating and a change in the basal metabolic rate.

Since I shall deal largely with lesions of the adrenal cortex, I wish first to say something about the classification of adrenocortical syndromes. A classification that is as satis-

factory as any is the one proposed by Kenyon.[1] He recognized six types of clinical syndrome, namely (1) adrenogenital syndrome, (2) Cushing's syndrome, (3) mixed clinical pictures including features of the first two, (4) a type characterized by single or isolated endocrine manifestations, (5) feminizing syndromes, that is, feminization of men or homologous sexual precocity in girls and (6) tumors without endocrine manifestations. Kepler, Sprague, Mason and Power[2] have discussed the characteristics of these syndromes. It should be said here that in an appreciable number of the cases the clinical manifestations do not conform to any of the foregoing clinical syndromes, and hence these cases defy precise classification.

I shall discuss hyperfunctioning lesions of the adrenal cortex, including tumors and hyperplasia and hypertrophy.

Adrenal glands that are the site of cortical tumors vary in size. In a group of 46 cases the weight of the glands ranged from 6 to 10 gm. The other day I removed two glands that weighed 14 gm. each, the patient having severe Cushing's syndrome.

Occasionally a cortical tumor is malignant even though it has not extended beyond the capsule. Unfortunately, sometimes the carcinoma has extended through the capsule and invaded adjacent tissue. I remember one such patient from whom I removed most of the tumor, which was on the right side, but I could not remove some of it from the undersurface of the diaphragm and the inferior vena cava. Although the patient got temporary regression of all her signs and symptoms, she had recurrence of them in six months with recurrence of the tumor (figure 1).

When one deals with enlarged adrenal glands or even with normal-sized adrenal glands (curiously enough, sometimes the glands may be of normal size in Cushing's syndrome) they are practically of proportionate size; that is, if one is enlarged the other is enlarged. That is how the patient who has Cushing's syndrome differs from the patient who has a hyperfunctioning cortical adenoma or a hyperfunctioning carcinoma of one adrenal. In the latter patient the opposite adrenal is small and atrophic. Thus, if you make a unilateral posterolumbar incision (we usually make bilateral incisions) and encounter an abnormally small gland on one side you know that there is a tumor in the other gland. A small section from such a gland will show characteristic hypoplastic changes when studied microscopically.

I want briefly to give you an idea of the his-

FIGURE 1. Patient with adrenocortical carcinoma.

a. Before the onset of adrenocortical syndrome.

b. At height of syndrome.

c. After removal of right adrenal tumor.

d. After recurrence of tumor.

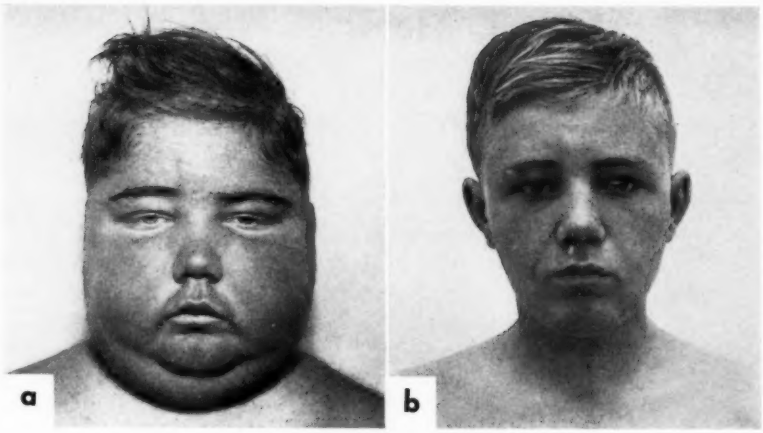

FIGURE 2. Patient 13 years old with Cushing's syndrome.

a. Before operation.

b. Thirteen months following left subtotal and right total adrenalectomy.

tory of a child, 23 months old, who had a hyperfunctioning adrenocortical tumor. She had precocious menstruation, hirsuties about her external genitalia, precocious behavior and a left suprarenal cortical tumor. Four months after operation these abnormalities had, for the most part, righted themselves but the child was still shy. This is rather characteristic of the behavior of these patients, as Dr. Conley and Dr. Randall will mention, and it frequently is a very important sign. Some of the patients with Cushing's disease have had so much depression that they have been institutionalized before they have had subtotal adrenalectomy.

One child, 17 months old, had a combination of urogenital symptoms and Cushing's syndrome. At operation an encapsulated adrenocortical carcinoma was removed.

Dr. Randall, would you like to say something about this case?

DR. R. V. RANDALL: This girl had had symptoms for about a year before she was brought to the Mayo Clinic. Her family thought she was just a good eater and that she had merely eaten a lot, until she began to have hirsutism, acne and a very characteristic Cushing's facies. I believe, Dr. Walters, that it has now been about four years since her operation, and she has had no recurrence of her carcinoma. She has had a good result and is a perfectly normal girl. She had a tumor on one side, which meant that the adrenal gland on the other side was normal; so, we expect her to have a normal future.

DR. WALTERS: The next case is that of a boy with Cushing's syndrome (figure 2). You will notice how characteristic his appearance is. He has a round face and his trunk was rather obese for a boy 13 years old. He had striae in the skin of the abdominal wall, acne and muscular weakness. All of these conditions were reversed in a short time after operation. Then he was well for three years. I had left what I thought was a third of his left adrenal, with total removal of the right. His symptoms recurred three or four years after operation and one of my former first assistants, Dr. Cleveland, took out the remnant of the left adrenal, which had hypertrophied considerably, and the patient has been well since. I believe this is one of the first cases of total adrenalectomy for Cushing's syndrome.

Figure 3 shows a young man of 17 years from whom I removed a hyperfunctioning suprarenal cortical adenoma. Subsequently, this boy was in an automobile accident out in Utah and nearly died because he had been taking supplementary cortisone but didn't have any identification card, such as the diabetic taking insulin has or should have, to indicate that he was taking cortisone. He went into shock immediately after the accident and was in coma for several hours before the ad-

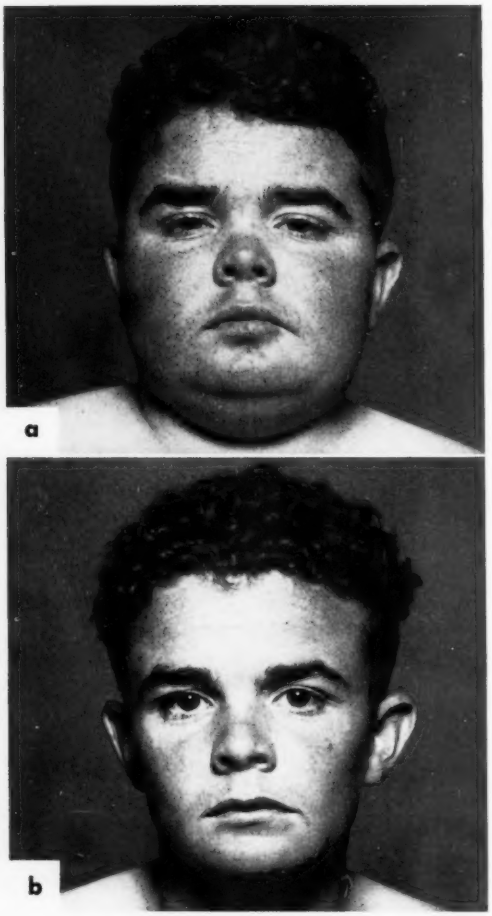

FIGURE 3. Patient 17 years old with Cushing's syndrome.

a. Before operation.

b. Twelve months after left subtotal and right total adrenalectomy.

renocortical deficiency was recognized. When intravenous normal saline solution and cortisone were given, he regained consciousness and recovered.

Do you have any comment on this case, Dr. Randall?

DR. RANDALL: No, I don't, Dr. Walters, but I think it is important to point out in this connection that most of the children, as a matter of fact all the children, who have been seen either at the Mayo Clinic or elsewhere because of Cushing's syndrome and who have been less than 10 years of age have had tumors. A good many of these have been carcinomas. Therefore, if this syndrome occurs in a child I think you can feel pretty certain that it is due to a tumor. That is not true during the teen ages, when the child may have either a tumor or hyperplasia.

DR. WALTERS: The next case is that of a woman, 36 years old, who had Cushing's syndrome. In 1942 she had amenorrhea. In 1946 there was onset of hypertension, fullness of the face and neck, hirsutism, facial rubor, thinning and dryness of the skin, and thinning and coarsening of the hair. In January 1948 she underwent bilateral sympathectomy elsewhere for hypertension, without benefit; adrenal hypertrophy was observed at operation. In September of that year she experienced marked weakness followed by mental depression and loss of libido.

In February 1949, when the patient was seen at the Mayo Clinic, her blood pressure was 200 mm. of mercury systolic and 140 diastolic, and she presented the typical appearance of Cushing's syndrome (figure 4a). The value for corticosteroids was 1.49 mg. and for 17-ketosteroids was 12 mg. per 24 hours. On March 12, three-fourths of the right adrenal gland, which was normal in size (2.1 gm.) and in histologic appearance, was removed; there was no improvement. On May 27, three-fourths of the left adrenal, which was normal in size (1.8 gm.) but had a hyperplastic cortex, was removed; there was no clinical change.

On June 24, 1949, the remainder of the right adrenal, which weighed 2 gm., was removed. This was followed by clinical improvement (figure 4b and c). The blood pressure dropped from 200/140 to 132/98, and the value for 17-ketosteroids decreased to 1.7 mg. and for corticosteroids to 0.33 mg. per 24 hours. In August, x-ray therapy was given to the pituitary body. A letter received in August 1950 indicated that the patient was well clinically. She returned to the clinic on October 15, 1951, for a checkup. Her appearance was normal. There had been a rise in blood pressure to 174/116. But the values for 17-keto-

FIGURE 4. Woman 36 years old with Cushing's syndrome.

a. Before operation. b. After operation. c. After operation.

steroids and corticosteroids had remained about the same as at the time of her dismissal, being 2.3 mg. and 0.94 mg. respectively for 24 hours. A letter in December 1955 stated that this had been a good year for her.

The next is a typical case of Cushing's syndrome (figure 5). The patient's appearance returned to normal and she was relieved of most of her symptoms after subtotal adrenalectomy. She underwent total removal of the left gland because she had recurrence of symptoms after its subtotal removal. A subtotal right and left adrenalectomy had been done more than eight years previously, and total excision of the remaining portion of the left adrenal gland was performed two years and five months ago. I had an announcement of her wedding just a few days ago.

I will now ask Dr. Conley to present his patient.

FIGURE 5. Patient with Cushing's syndrome.

a. Before operation.

b. After operation.

DR. JAMES E. CONLEY: The patient I wish to present had an adrenal medullary tumor which was removed in March of 1953. He had sustained hypertension since 1950 when it was noted during a routine examination. Of significance is the fact that in 1948 he had an operation, at which time the blood pressure was normal. During the interim of three years he had this sustained hypertension and his symptoms were as follows: First, he had what he called "waves of weakness" when he would be doing some work and he would suddenly have a weak spell and he would have to bear with it for a couple of minutes and then it would subside spontaneously. These occurred every two or three weeks. Secondly, he perspired quite profusely and several people noted it, including his barber, who advised him to see a doctor because he perspired abnormally. Third, he had intolerance to heat. During the summer of 1952, before his operation, he had a very miserable time; even though he was in the air-conditioning and refrigeration business, he was quite miserable because of his intolerance to heat.

During the winter he also was quite intolerant to heat, frequently checking the thermometer in his home to see whether the temperature was abnormally high, and opening windows during the middle of the winter.

He was admitted to the hospital, and he had a sustained hypertension. I might just briefly quote some of the blood pressure figures. His lying blood pressure was 206/132, and his standing blood pressure was 182/140. He reacted normally to cold pressor tests. He had a positive REGITINE® test; 5 mg. of Regitine injected intravenously lowered the systolic pressure 40 mm. and the diastolic pressure 35. Also, he had a positive benzodioxane or piperoxan test.

DR. WALTERS: May I interrupt you a minute? These tests which Dr. Conley has just mentioned are very important in the study of these cases. The substances used lower blood pressure under circumstances of medullary stimulation. Do you want to say a word for or against the histamine test?

DR. CONLEY: In general the histamine test should not be used in sustained hypertension, because if the test is positive one gets a marked rise of blood pressure which may cause a hypertensive crisis with pulmonary edema; so, the histamine test is contraindicated in patients with sustained hypertension. The Regitine or piperoxan test is used when there is a sustained hypertension.

The significant laboratory studies revealed a basal metabolism of plus 22; he had definite hypermetabolism; he had a urea clearance of over 100 per cent, one of those unusual conditions which may produce a urea clearance of over 100 per cent; his was 110 per cent. The electrocardiogram and chest x-ray were within normal limits, except for a tachycardia, which is a common feature with this tumor.

In March 1953 he had the tumor removed from the left adrenal through a posterolateral incision. The tumor was localized by means of a laminagram. He had a variable blood pressure during the course of induction and during the course of manipulation of the tumor, which presented a very serious situation at the time of operation. Immediately following operation, the blood pressure became imperceptible and it was necessary to use pressor drugs. NEO-SYNEPHRINE® and ARTERENOL® were used. Also, he had transfusion to replace the blood loss.

For 36 hours his blood pressure had to be sustained with a slow infusion of Arterenol, and whenever this was stopped his systolic blood pressure dropped below 100 mm. of mercury.

Convalescence was uneventful otherwise. He was out of bed the second day and discharged on the twelfth day.

The laminagram fortunately localized the tumor in the left adrenal area in the x-ray at depths of 8 and 10 cm. The tumor was readily visualized, especially at the 8 cm. level.

The adrenal tumor measured 5 cm. in diameter and weighed about 16 gm. It was assayed and found to contain 3.1 mg. of norepinephrine and 0.8 mg. of epinephrine.

DR. WALTERS: Thank you very much, Dr. Conley. I think you presented the case very well indeed. Would you ask the patient to comment on his symptoms.

DR. CONLEY: Would you describe your reaction preoperatively and after the operation?

PATIENT: All I can say is that I feel pretty good. This may not sound important to you, but I was sitting in the middle of the room here for about two minutes and I didn't move around and wasn't nervous and jumpy. As far as I am concerned the operation did it, because I used to sit in sales meetings and drive the sales manager nuts by squirming around. I couldn't sit still for five seconds, much less five minutes.

DR. WALTERS: How about the sweating? Did you mention that?

PATIENT: No, I didn't. As I told the doctor before I came in here, it is a pretty cold day outside and before the operation, cold or not, I used to perspire night and day.

DR. WALTERS: What did your barber say?

PATIENT: "Go home and see a doctor."

DR. WALTERS: Some real cooperation here in Milwaukee. Thanks very much.

If time permits I would like to say a few things about pheochromocytomas, but before doing so I will ask Dr. Randall to give us a little discussion of Cushing's syndrome.

DR. RANDALL: When Cushing first described the syndrome in 1912 and wrote his paper in 1932, it was felt that Cushing's disease and syndrome were secondary to pituitary tumors. But more recently, especially since the advent of cortisone and since doctors have found that administration of cortisone will give all the signs and symptoms of Cushing's disease, it has been realized that the adrenal plays a pretty important role. The present concept is that the adrenal is the gland primarily at fault.

The role of the pituitary in Cushing's disease is still unknown. Two concepts predominate at present. The old concept, which still has not been entirely abandoned, is that the pituitary, for some reason, functions abnormally and stimulates the adrenal gland to secrete large amounts of steroids and cause Cushing's syndrome. It has been found that if one gives large amounts of steroids to normal animals or to human beings, one can also cause changes in the pituitary. Consequently, the second concept has arisen: namely, that the adrenal gland is primarily at fault and by producing large amounts of steroids causes Cushing's syndrome and the changes in the pituitary which are usually seen at necropsy.

I thought I might discuss some of the salient features of Cushing's syndrome, because one of the largest problems we have is making a differential diagnosis between the woman who is slightly overweight and who has a slight increase in blood pressure, hirsutism and perhaps diabetes and the woman who has Cushing's syndrome. I think that for every woman we see with Cushing's syndrome we must see at least 10 or 12 women who have obesity and physiologic hirsutism; so, it constitutes a rather large problem.

Among the signs and symptoms of Cushing's disease, there is nearly always rounding of the face, as Dr. Walters showed you. Hypertension is very common, and of the 100 patients operated on from July 1945 to June 1955, 90 had hypertension. Truncal obesity, as Dr. Walters pointed out, is very important, too, and is one of the common characteristics. The obesity really is confined to the trunk; the arms and legs do not enlarge. As a matter of fact, some of the patients have mentioned that their arms and legs have become smaller. Also, as you well know, almost everybody who has a big stomach has a big posterior—most of these patients have a small posterior.

Redness of the face, hirsutism, enlargement of the fat pad over the cervicodorsal region, purple striations and acne are also very common. These people have changes in the skin, and as a consequence they have ecchymoses and purpura. Amenorrhea is very common.

Laboratory findings that are of importance and help us in making a diagnosis are lymphopenia and hyperglycemia. A good many of these patients have true diabetes, which often disappears after surgery on the adrenals.

Very commonly they may have an alkaline urine, low serum potassium, alkalosis and hypochloremia.

Polycythemia and an increase in the blood sodium have been reported in the literature as common findings. These have not occurred frequently in our experience. Most of our patients have not had these changes.

Dr. Walters, you mentioned surgery as the treatment of choice for this syndrome. I wonder if you would tell us a bit about your results and your experiences in treating this syndrome surgically.

DR. WALTERS: Since we have only about half a minute, Dr. Randall, I believe I will forego a discussion of results except to say that the mortality rate in 100 of these cases has been 7 per cent—that in subtotal adrenalectomy for Cushing's syndrome the results have been excellent. We now have patients who were operated on more than five or six years ago, have we not?

DR. RANDALL: Some as long as 10 years ago.

DR. WALTERS: So we know that this disease, which, unless surgically corrected, usually eventuates in death of the patient, can be held in abeyance with the surgical procedure that has been mentioned.

In closing, I want to say a word about pheochromocytomas. In our group of 48 patients with pheochromocytoma we have had 58 tumors. In four of the patients the tumors were bilateral, and in one they were multiple (ribs and neck), so that my colleague, Dr. Priestley, and I think the best incision is the transverse upper abdominal one that permits both adrenals to be examined. We do not use that incision for subtotal or total adrenalectomy, in which we think the posterolumbar incision is best.

THE SPEAKER: In order to keep this organization up to date, there is one title which Dr. Walters has that I did not tell you about. He is a new Rear Admiral in the medical corps of our United States Naval Reserve.

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Postgraduate Clinical NOTES

55. SYMPTOMS OF GASTRIC CANCER

The type of symptoms in gastric cancer depends upon a number of factors such as type and size of tumor, site, presence of free hydrochloric acid in the stomach, and tendency of the lesion to ulcerate, bleed, or metastasize. There is no single symptom pathognomonic of gastric cancer, but certain symptoms are suggestive. Among the symptoms of early gastric cancer are change in tolerance of food, postprandial vague dyspepsia, flatulence, eructation, and nausea. According to Cooper, change in tolerance of food is the most common initial symptom. Bruce notes that patients with so-called irregular dyspepsia syndrome commonly first experience epigastric discomfort in the form of a slight cramp or burning sensation after a heavy or unusual meal. Later there appear a sense of fullness, belching, and a tendency toward regurgitation. In some patients, early satiation is the first symptom, with later capriciousness in appetite, and eventually complete distaste for or even frank nausea at the sight or taste of food.

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Both-bone Fractures of the Leg

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BOTH-BONE fractures of the leg are frequently mishandled because the basic principles of this very common injury are not clearly understood. Many times we treat fractures from memory of what someone else said or wrote; consequently we forget some of the details.

Most of the muscles of the leg have their origin in the lower portion of the femur and their insertion in the foot (figure 1). The inherent property of muscle is contractility; it is working 24 hours a day; it is working against gravity, against your pull, against a Steinmann pin traction. One must constantly bear that in mind when treating both bones of the leg.

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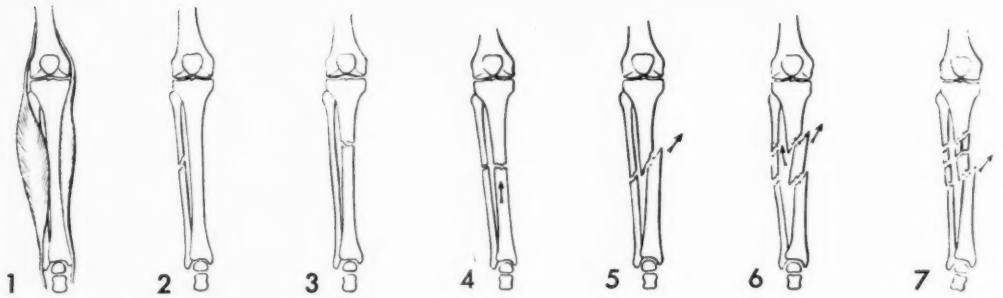
Figure 2 illustrates the simplest type of leg fracture, a fracture of the fibula with the tibia intact. Displacement will not occur here. The patient will have some pain if he uses the leg in walking, but he cannot get any shortening or angulation. With an intelligent patient, one can obtain an excellent result merely by telling him to stay off the leg for about six weeks and use crutches. A child or an uncooperative adult is better off with a cast from the lower third of the femur down to the toes, with a walking iron in the cast.

The fracture shown in figure 3 is more complicated. The fibula is intact; it splints the fractured tibia at both ends, so that shortening cannot occur, but there can be some motion at the fracture site which produces pain and there can be a certain amount of angulation. Because of the element of pain and the possibility of slight angulation, this type of fracture is best treated with a long leg cast, probably from the middle third of the femur down to the toes. A walking cast is permissible, since shortening cannot occur.

Figure 4 shows a still more complicated



FIGURES 1 to 7. Diagram showing: 1. Tibia, fibula and muscles of the leg. 2. Fracture of the fibula with the tibia intact. 3. Fracture of the tibia. 4. Transverse both-bone fracture of the leg. 5. Oblique fracture of the tibia with a fracture of the fibula. 6. Both-bone fractures with intermediate third fragments. 7. Comminuted both-bone fractures. Under no circumstance should there be any weight bearing on the fractures shown in figures 5, 6 and 7.

problem, a transverse both-bone fracture. There are interdigitations of the fracture line. The bone cannot get out of place but it can angulate and produce a lot of pain. Shortening will not occur. A patient with this type of fracture requires only immobilization in plaster from the middle third of the femur down to the toes. Because the fracture is transverse, after the original swelling has diminished and the pain abated, a new cast may be applied and walking permitted with a walking iron.

An oblique fracture of the tibia with a fracture of the fibula is seen in figure 5. There is no stabilization here. Regardless of what one does, this fracture is going to shift; there will be overriding and shortening. Therefore, the basic principle in treatment is traction to maintain length. We have found that it is infinitely better in these cases to operate as soon as the patient's condition and skin permit and to perform fixation, preferably with two screws or a plate. Keeping this patient in a cast may provide good position for 48 hours, but then the bone will shift. Skeletal traction necessitates keeping him in bed at least six to eight weeks, and good control of this fracture is impossible by this means—it seems to get out of position every time the patient is moved.

This type of fracture can be treated by double pin fixation, inserting a pin through the upper end of the tibia and one through the lower end of the tibia or the os calcis, reducing them on a Baylor frame and then incorporating them in plaster. However, that procedure, which we used many years ago when it was first popularized, has led to many problems. In 1935 at the County Hospital in Chicago we had an incidence of delayed union and nonunion of 35 per cent. That is much too high.

The fracture in figure 6 represents a really complicated problem. There are intermediate third fragments, there is displacement, and invariably, in our experience, one end or the other of the tibial fracture goes on to nonunion. I feel now that in this type of case it is best to operate and immobilize. Formerly I used plates in these cases, but immobilization required a long plate on the fibular side of the tibia. Now, with intermedullar pinning the results are very satisfactory. The Rush pin has proved very suitable in this type of case. I have not used the Lotti pin that has been devised in St. Louis, with which the reported experience has been excellent.

Of course, one could treat this fracture by skeletal traction in the os calcis or by double pin fixation in a cast (one through the upper end of the tibia, one through the lower end of the tibia or os calcis), but I prefer intermedullar pinning.

The fracture shown in figure 7 is a real problem. It is axiomatic that the more comminuted a fracture is, the less is the indication for surgery. In our experience these are best treated by skeletal traction in the os calcis,

with the patient in bed for six to eight weeks, later treated by a cast.

Under no circumstances should there be any weight bearing on the fractures shown in figures 5, 6 and 7.

Spiral fractures of the tibia are, I believe, primary indications for open reduction (figure 8). As soon as the condition of the skin permits, I would operate.

Figure 9 shows two screws in place for fixation. One can get anatomic reduction. The pain is decreased, the hospital stay is shortened, and there is no deformity whatever. Some years ago we reported 78 cases with no failures.

Figure 10 illustrates another spiral fracture. Invariably either one end of the fracture or the other gets into the soft tissues. When I was Dr. Cubbins' resident at the County Hospital I was the fellow who was always at the end holding the leg and pulling. Dr. Cubbins would say, "Come on, pull, Carl, you have only a quarter of an inch to go, a half inch to go. Come on, Carl, pull!" By the time we were through, I needed a transfusion instead of the patient. All the fellows I am associated with are about my size, so we put these patients on a fracture table and let the machinery pull down the leg.

The postoperative reduction is shown in figure 11.

A spiral fracture with some overriding is shown in figure 12. Anatomic reapposition was obtained by operation (figure 13).

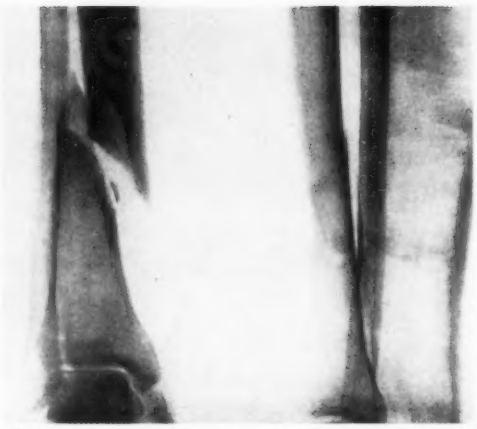


FIGURE 8. Spiral fracture of the tibia, an indication for open reduction.

FIGURE 9. Two screws in place. Anatomic reduction.

FIGURE 10. Spiral fracture of the tibia.

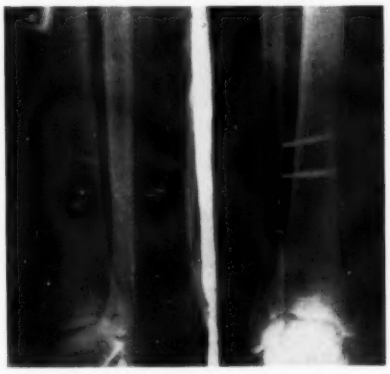


FIGURE 11. Good postoperative reduction of fracture.

FIGURE 12. Spiral fracture of tibia, with some overriding.

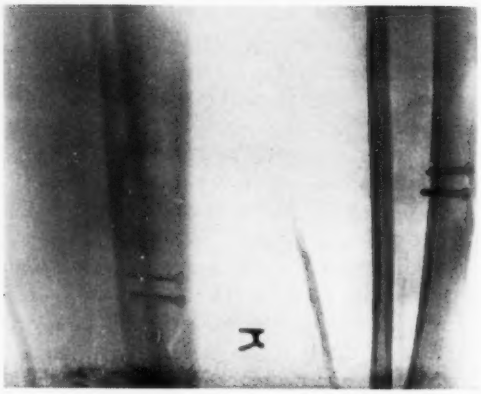


FIGURE 13. Anatomic reapposition following operation.

FIGURE 14. Complicated case of both-bone fracture of the leg.

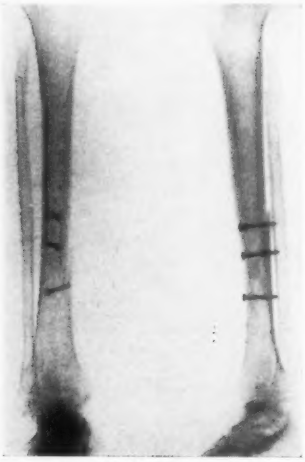


FIGURE 15. An anatomic reduction was achieved.

The fracture in figure 14 is rather complicated. Not only is the fracture of the tibia oblique, but there is the appearance of a fracture line running down the shaft. If one is not careful in screwing that together and putting on clamps, it will split. An anatomic reduction was obtained, as shown in figure 15.

I want to bring out a point with which you are all well acquainted. When doing a both-bone fracture of the leg, do not waste time on the fibula, with very few exceptions. Stay on the tibia; if you reduce it, the fibula will fall in place.

Figures 16 and 17 illustrate a fracture which was plated. In plating a tibia, it is very important to plate it on the fibular side; you can cover it with muscle, it is out of the way, it is not subcutaneous, it is not always going to be bumped, and often you will not have to remove the plate. Sometimes, because of available facilities or compound wounds and so on, you might want to plate it on the medial side, but it is then subcutaneous, it is going to give you trouble, and you will have to remove it. I prefer, if I have a choice, always to plate it on the fibular side that I can cover with muscle.

There is considerable angulation in the compound fracture shown in figure 18. The patient was struck by an automobile. The primary plating is shown in figure 19. I like to use the T & G plate. It is semipliable, has

FIGURES 16 *(left)* and 17 *(right)*. Plating was done in this case of fracture. This procedure gives best results when the tibial plate is applied on the fibular side.

ovoid holes and can be bent without breaking. These plates nest together very well and one can make the plate as thick as one wishes. It is very serviceable. It comes in various lengths and you can cover an area of 12 to 14 in. with several plates, one on top of the other.

Another spiral fracture, a short spiral, is shown in figure 20. In this case, some people might say, "Let's treat this in a cast; it will go along all right." It will, until muscle spasm occurs, and then there will be overriding. The end result, with plating, can be seen in figure 21. Notice that a transfixion screw was used. Sometimes it is important, after one has plated a fracture and it seems to spread a little bit, to put an oblique screw through the fracture line to immobilize it completely.

In the compound fracture shown in figure 22 the bone protruded out through the soft tissues. This brings up a point that is frequently forgotten. The skin was greatly macerated due to the compounding. After débridement, we carefully opened up the fibula, which was not compounded, and plated it. We obtained excellent immobilization, the foreign material was away from the compounded area, the skin was not jeopardized by the addition of metal underneath it, and solid union resulted (figure 23). In the past few years I have done about four cases by plating the fibula because the skin over the tibia was badly damaged. When I was in the armed services in Richmond, Virginia, during the Battle of the Bulge we got about 10 or 12 cases of compound gunshot wounds at the tibia—pieces blown out, the skin badly damaged—and in every one of these cases the fibula was plated. The results were excellent. Remember that if the skin is badly damaged over the tibia, do not put any foreign body there. Use the fibular side and you will be safe.

The oblique fracture in figure 24 does not appear too serious, but if left alone it will cause trouble. Figure 25 shows a Rush pin in place. I would say we probably got down to the last osteophyte between the joint and the end of the pin. I do not like being that accurate; I like to leave myself a little more room. No matter how carefully you measure these pins and the length of the tibia, you always end up, as Dr. Homer Stryker of Kalamazoo says, by calculus. We learn from experience. Measure to the best of your ability, put in the pin, and before driving it all the way home have an x-ray made in the operating room. You will be surprised how far that pin is from where you think it should be.

I always tell the story about an elderly lady who had a severe fracture of the femur. We were just learning how to use the Kirschner pin, and we put it in. The next day the patient said, "The fracture is wonderful, but the arthritis in my knee has flared up since you operated." We made an x-ray and found that the pin was about an inch into the joint. The following day we told her we had a specific cure for arthritis—we thought we could cure it with some special medicine, but we would have to give her some gas. We pulled the pin out of the joint and the pain disappeared.

Figure 26 shows a severe compound comminuted fracture. We also used a pin in this

FIGURE 18. Compound fracture, considerable angulation.

FIGURE 19. Primary plating.

FIGURE 20. Short spiral fracture of the tibia.

FIGURE 21. End result with plating.

FIGURE 22. Compound fracture.

FIGURE 23. Excellent immobilization provided by plating. Solid union resulted.

FIGURE 24. Oblique fracture.

FIGURE 25. Rush pin in place.

case. Perhaps the pin should have been a little longer, but the end result was excellent. There was some delay in healing. The x-ray in figure 27 was taken about eight months later.

There are three patients here whose cases I will describe briefly. The first is a 67 year old man who sustained a compound fracture of the right leg on October 30, a couple of weeks ago. Débridement was carried out at Milwaukee General Hospital under general anesthesia, and no form of internal fixation was used. He has a long leg cast, from the toes to the middle third of the femur. The general alignment of his leg appears to be good. The x-rays present a problem as to his future course. Those taken immediately after operation show some forward displacement of the tibia, the distal fragment, and the ankle mortise is not quite at right angles to the long axis of the leg. There has been some shifting laterally.

An x-ray taken after he was wedged still shows slight displacement of the distal fragment anteriorly, but the general weight-bearing line of the tibia is satisfactory and the ankle mortise or the distal articulation of the

FIGURE 26. Severe compound comminuted fracture. A pin was used in this case also.

FIGURE 27. Result about eight months later.

tibia appears to be at right angles to the long axis of the leg. There has been considerable improvement over the previous appearance. Some angulation still is present. The fracture in this case is too close to the ankle to consider any type of internal fixation, and my only recommendation is that, if the wound is clean, perhaps it might be advantageous to angulate the leg slightly in a medial direction when the cast is changed, before the bone solidifies. It is very important to have the ankle mortise at right angles to the long axis of the leg; otherwise, abnormal wear and tear of the joint result.

The next patient, a 33 year old man, sustained a fracture on November 5, 1954. On February 4, 1955, operation was performed because of nonunion, and a sliding bone graft was applied. At present, nine months later, the patient still has nonunion. Outwardly, he appears to be in excellent physical condition, and that brings up the problem of the causes of nonunion. I wish we really knew what they are; we know some of them but not all.

There was a great deal of displacement in his case. Lateral and anteroposterior x-rays taken following correction show that general alignment was good and that the weight-bearing line was satisfactory. He has anatomic reapposition in the fibula, as far as we can determine, and yet nonunion developed. A sliding bone graft was applied, extending a considerable distance, and two screws were inserted. Certainly he has enough fresh bone, he has good apposition, and yet he has nonunion.

It is very difficult to decide what to do in a case such as this, but certainly one has to reoperate. I would recommend removing the screws and probably taking a lot of iliac graft. One can get that succulent cancellous bone from the wing of the ilium and pack it on the lateral side between the tibia and fibula, and if a synosteosis results, so much the better.

I had one patient who came to me after having had two operations on both legs for nonunion. I operated three times, and he still has nonunion in both legs—five operations.

The third patient is a 43 year old woman who fell downstairs on October 12, a little more than a month ago. She had a short spiral fracture. Operation was performed on November 2, about two weeks ago. The general longitudinal alignment is very good. A cast was applied at first, and slipping occurred. One cannot treat these cases with casts; muscle spasm pulls the bone out of place. At operation, plating was done, and the results appear to be excellent.

A question which these patients always ask is, "Doctor, when can I get up and go to work?" In this woman's case we know that it will be three or four months before she can get around without crutches or any external support.

QUESTION: Do you usually remove the plates and screws?

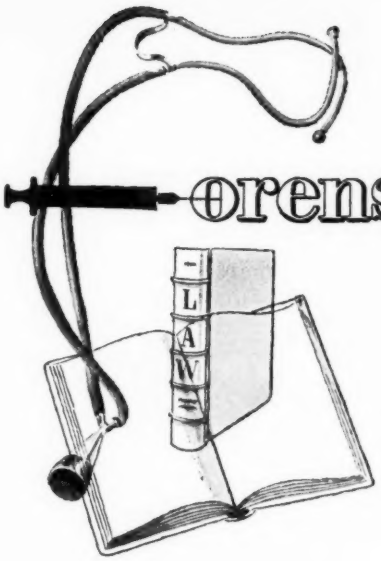
DR. SCUDERI: At present, with the standardization of metal used, we remove less than 10 per cent of the plates. The only indication for removal is infection or irritation because the plate is so superficial that it rubs against the skin. Otherwise we leave them in.

QUESTION: In the case you described with nonunion in which you suggested the iliac graft, what type of fixation would you employ?

DR. SCUDERI: This man has a good fibrous union between the bone ends. There will not be any overriding. He is going to have angulation, so if you pack those bone chips along the lateral aspects of the tibia, all he requires for postoperative immobilization is a cast from the toes to the middle third of the femur.

QUESTION: If there is not enough angulation at the knee with the cast, is there not a danger of nonunion?

DR. SCUDERI: I am sure you meant the bending of the knee—if there is not enough angulation is there a danger of rotation and nonunion? We prefer putting the knee in about 10 to 15 degrees of flexion. That is a little more comfortable for the patient and does add some element of prevention of rotation, but it would not contribute necessarily to nonunion. All it would contribute to would be a malunion, and the patient would be toeing in or out, depending on the position of rotation. I feel they are best treated with about 15 degrees of flexion at the knee.



Forensic Medicine

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The Role of Photography in the Coroner's Office

S. R. GERBER*, LESTER ADELSON† AND LAWRENCE JOHNSON‡

Coroner's Office, County of Cuyahoga, Cleveland

THE tasks confronting medicolegal investigating agencies are as varied and intricate as twentieth century civilization itself. They include evaluation of the many factors involved in the huge number of traffic fatalities that occur annually in metropolitan jurisdictions, the analysis of industrial hazards that require the full-time attention of safety engineers, and the investigation of a great many chemical and immunologic problems. These are in addition, of course, to the homicides, suicides, accidental deaths, and deaths from other causes that were familiar to the coroner of a century ago.

Whenever the apparent cause of death or the circumstances involved indicate that a fatality may have resulted from the negligent or deliberate act of either the victim or another person, inquiry into the details must be made by a competent medical public official. The same is true of sudden and unexpected natural deaths and of any deaths possibly due to some unrecognized threat to public health. The eradication of threats to health and life frequently depends on the precise pinpointing of the circumstances involved in an obscure death through the efforts of the coroner and his staff.

The purpose of these medicolegal inquiries is to establish the exact cause and manner of death. For this reason, the acquisition and documentation of accurate and unbiased evidence are essential if justice is to be assisted in criminal and civil proceedings. In the study and presentation of this evidence, the present-day coroner utilizes information and technics obtained from a wide range of intellectual dis-

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ciplines: pathology, chemistry, toxicology, radiology, anthropology, dentistry, entomology, botany and many others. The use of a considerable variety of precision instruments is required, including microscopes of many kinds, x-ray diffraction cameras, infrared and ultraviolet spectrophotometers, measuring apparatus of all types, and radiographic and photographic equipment. This article shows how photography materially aids the coroner in discharging his responsibilities.

Need for Photography in the Coroner's Program

The photographic camera, loaded with color film, is among the most commonly used and valuable pieces of equipment in the coroner's office. Since the coroner deals with highly perishable material, he must be in a position to record permanently and accurately the appearance of a body or organs at the time of examination. Actually, the photographic record supplements and complements, but does not supplant, the complete verbal description. Rarely, however, will the words of the individual who describes the signs of injury or disease be as graphic or compelling as a well-made color photograph of the subject.

Anatomic pictures, however, represent but a fraction of the use of photography in medicolegal work. Photographs of ancillary evidence, such as bullets or clothing, in or on a body, or of other material having some bearing on the cause and manner of death, also assist in documenting an inquiry.

The value of photographs, moreover, goes far beyond their use in cases under investigation. Such photographs, together with other data and material accumulated at the coroner's office, can be of benefit to many professional groups and individuals: medical students and practicing physicians; law students and practicing attorneys; coroners and medical examiners; police academy trainees; police investigators and law enforcement officials; postgraduate students in law, medicine and police science; insurance claims adjusters; newspaper reporters; and agencies for public health and public safety. The importance of such visual aids in the medicolegal indoctrination and training of these various groups cannot be stressed too strongly.

The presentation of the work of the coroner's office to interested lay groups and service organizations is another function immeasurably aided by well-documented cases illustrated with color transparencies. Such public relations and educational activities are important to the coroner's program, because they enlighten the community and make it possible for him to obtain necessary public cooperation. Inasmuch as death may strike suddenly, unexpectedly, or violently anywhere, it is essential that the entire community be aware of the coroner's duties, responsibilities and authority. In this way, people will not be confused or apprehensive when the death of a friend or relative is investigated. Unfortunately, there is a widespread misconception that when the coroner takes jurisdiction over a body there is necessarily something illegal or suspicious connected with the death, and that a stigma is attached to any death considered by the coroner's office. Experience in Cleveland has shown that more than 60 per cent of all deaths certified by the coroner are the result of natural causes, 24 per cent are accidental, 8 per cent suicidal, 4 per cent homicidal, and the remainder due to violence of undetermined origin.

Research into the causes of manifestations of sudden and unexpected natural and violent death also is an invaluable by-product of the daily work of the modern medicolegal office. Gross specimen photography and photomicrography are integral parts in the presentation or publication of the results of such studies.

Examples of the Medicolegal Work of the Coroner's Office

The postmortem medicolegal investigation seeks to elicit from the body answers to five basic questions:

1. Who is this person?—the problem of identification.

2. When did this person die?—the establishment of the time of death or the range of time within which death may have occurred.

3. Did this person die of natural or violent causes?—determination of manner of death.

4. If this person died by violence, was it accident, suicide or homicide?—the questions of culpability and negligence that must be answered.

5. If this person was murdered, who did it?—the search for evidence, on and within the body, that will aid the apprehension of those responsible for the death.

Identification

For humanitarian, civil and criminologic motives, establishing the identity of an unknown body is a frequent and fundamental problem in postmortem medicolegal work. The family and friends of the deceased must be informed of the death so that the body may be claimed and properly interred in accordance with the deceased's religion. Payment of insurance death benefits, settlement of estates, probate of wills, and remarriage of a surviving spouse depend on establishing the identity of the body.

Besides the uses previously mentioned, photographs are valuable as portable records of evidence. Obviously, the actual persons or objects cannot always be available for purposes of identification or other reasons during an investigation.

Case example—A severely burned body was discovered in a burned-out bowling alley after the fire had been extinguished. The facial features, extremities and clothing were so badly damaged as to prevent identification by such ordinary procedures as sight recognition, fingerprinting, or the finding of name tapes or laundry marks on the clothing. Within the mouth there was a partially burned artificial upper denture. Embedded within the plastic portion of the denture was a strip of paper with the typewritten letters ". . . ghns" with part of a letter preceding the "g" (figure 1). The rest of the word had been destroyed. Starting with this information, investigation revealed that the victim's name was "Vaughns."

Time of Death

Establishing the time of death may have a direct bearing on determining the cause and manner of death. Photographic records are of major importance here.

FIGURE 1

Case example—A 70 year old man, known to have had coronary disease, was found dead in a burned room. Autopsy disclosed severe occlusive coronary arteriosclerosis and the presence of smoke particles in the trachea and major bronchi (figure 2). Analysis of the blood revealed 50 per cent saturation of the hemoglobin with carbon monoxide. The smoke in the air passages and the presence of large quantities of carboxyhemoglobin were proof that respiration had taken place in the fire, and that death was the result of the fire. Had death occurred from the pre-existing disease, neither of these findings would have been present. An insurance claim with double indemnity benefits for accidental death was paid.

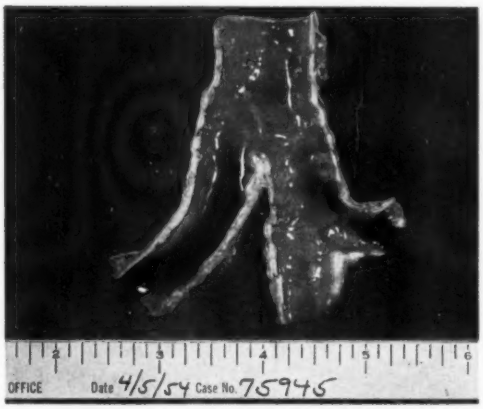


FIGURE 2

FIGURE 3

Manner of Death

Ample experience has taught that death from natural causes may masquerade as suicide, accident or homicide, and vice versa. In some deaths from natural causes, there may be abundant external injury with no significant internal trauma. On the other hand, fatal violence may be sustained with little or no external evidence to point to unnatural death. In the former situation, an innocent person may find himself under suspicion of homicide. In the latter instance, a murder may go unsuspected and undetected, or beneficiaries may be deprived of insurance benefits for accidental death or industrial injury. Death by poisoning is the unnatural fatality that most frequently presents no external evidence of what has transpired. In the interest of public welfare and the administration of justice, it is vital that the exact manner of death be established in all such doubtful cases. Photography is particularly valuable in documenting the appearance of a body before transient or irreplaceable evidence is destroyed during the investigation.

Case example—A 60 year old moribund man was admitted to the hospital with clinical evidence of cerebral damage and multiple bruises over the body. Death occurred before diagnostic studies could be completed. Relatives stated that the deceased had engaged in an altercation two days previously and had been knocked down. The police promptly arrested the other person involved in the fight. Autopsy showed subacute bacterial endocarditis and a ruptured mycotic cerebral aneu-

FIGURE 4

rysm (figure 3). There was no evidence of mechanical trauma to the skull or brain. The suspect was released.

Case example—The police brought the body of a 26 year old woman to the coroner's office. They stated that they had been notified of the death by her friends who had claimed that she had been ill for a long period of time, and that her physician was on vacation and thus not available to sign the death certificate. The police had found the body neatly arranged in bed in an apparently well-kept home which showed no signs of disturbance. At autopsy slight abrasions on the nose and breast were revealed. Internally, there was a laceration of the left cardiac ventricle with hemopericardium, and lacerations of the liver with hemoperitoneum (figure 4). The true nature of the death was immediately communicated to the police. Reinterrogation disclosed that the victim's paramour had killed her by jumping on her chest and abdomen with his knees. He had done this in the presence of onlookers and had threatened them with a similar fate if they gave any information to the authorities. They in turn attempted to pass off the death as one due to natural causes. The suspect was indicted and pleaded guilty to manslaughter.

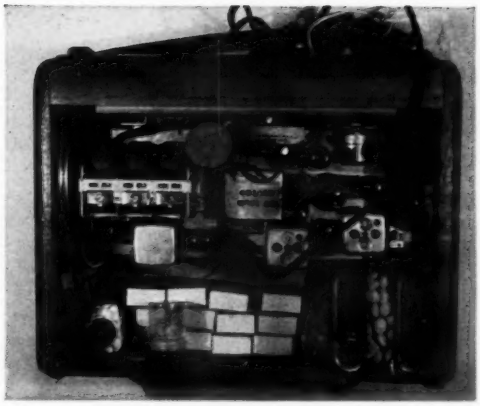
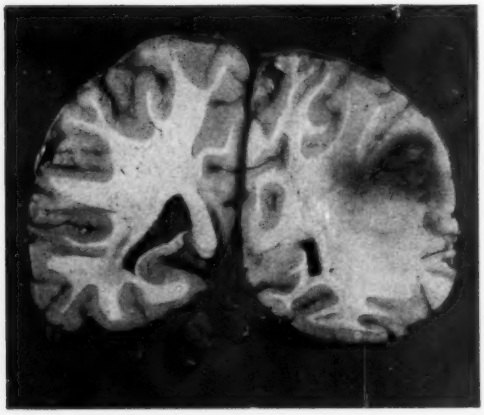


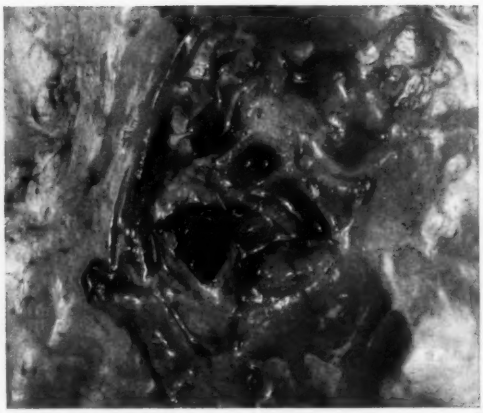
FIGURE 5

Case example—A 26 year old man, registered from an out-of-town address, was found dead in bed in a hotel room. Autopsy disclosed no evidence of natural disease or of injury, but chemical analysis of the blood and viscera revealed lethal quantities of barbiturate. Search of the personal belongings of the victim disclosed literally hundreds of barbiturate pills secreted in a portable radio (figure 5). Police investigation showed the deceased was a "barbiturate bootlegger." Death was the result of overindulgence in his own illicit merchandise.

FIGURE 6

FIGURE 7





Suicide, Homicide or Accident

Where death is the result of either known or unknown violence it is essential to determine the manner in which the injuries were sustained. Especially, when there were no eyewitnesses, or when witnesses tell contradictory stories, examination of the body and clothing, combined with the results of other avenues of inquiry, may well furnish the evidence of a correct reconstruction of what has transpired. Here also photography may play a major role in recording accurately the appearance of details that lead to a solution.

Case example—A 42 year old man was found dead with a shotgun wound of the lower part of his chest. The weapon was found a few yards from the body. Autopsy disclosed a contact type of entrance wound and extrusion of omentum through the perforation in the skin (figure 6a). The full charge of the shotgun, including the wadding, was found within the body. Examination of the pajamas worn at the time of the shooting showed blackening and burning of the fabric consistent with a contact wound (figure 6b). The case was ruled a suicide.

Case example—A seven year old girl was admitted to the hospital in an unconscious and convulsive condition. Her parents said that she had struck her head eight days previously when she had been knocked down by a playmate. On the day prior to admission, she had vomited several times and complained of headache. These symptoms were rapidly followed by convulsions, stupor and coma. Diagnosis of probable intracranial injury was made, and she was prepared for craniotomy. She died while the anesthesia was being administered. At autopsy, a brain abscess (figure 7a) and localized meningitis were found. The paranasal air sinuses and middle ears were free of disease. The source of the metastatic abscess was discovered in the right main stem bronchus in the form of a rusted safety pin surrounded by a localized zone of suppuration (figure 7b). Thus death was due to an accident, but not to that assumed originally. The accident responsible for the child's death occurred at some unknown time when the child aspirated the pin and failed to tell her parents about it. The importance of this type of case resides in its humanitarian implications. The little girl's mother had been extremely angry with the playmate, the child of a close friend, whom she had held responsible for a supposedly fatal accident. When the exact facts were related to her, she was relieved of the bitterness that had compounded her grief.

Responsibility for Death

On or within the body, there may be evidence that indicates directly those responsible for the death. A bullet recovered from a body can be traced to a particular firearm and thus

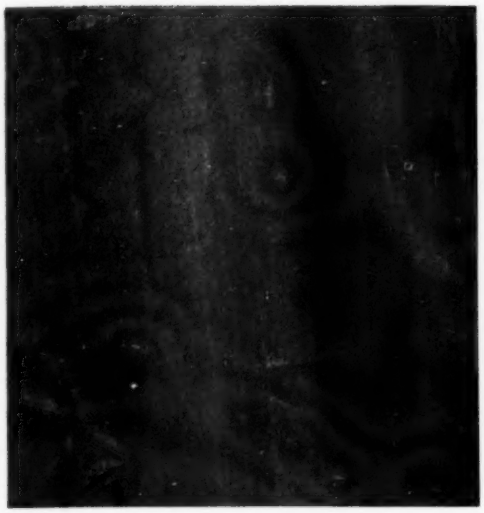


FIGURE 8

FIGURE 9

help to indicate the probable killer. Foreign bloodstains may provide valuable leads in tracing suspects. The many-sided role of photography in the laboratory in such instances is well known.

Case example—An unidentified body was found at dawn in an alley leading to a truck loading platform. The head had been crushed as though a wheel had passed over it. There were no other injuries. The pattern of two tire treads was distinctly imprinted on the victim's blue suit (figure 8). The police traced every truck that had used the loading platform during the preceding 12 hours and found only one whose tires matched the marks on the clothing. The driver, a man with an excellent record, admitted that he had felt a bump as he drove out of the alley in the early hours of the morning. However, the surface of the road was rutted and irregular, and he had ascribed the bump to the poor condition of the driveway. He stated that he had not seen anyone and had not suspected that he struck the victim. The fact that the injury was confined to the head was taken to indicate that the victim had been sleeping in the road and had not been knocked down by the truck. This opinion was strengthened by a blood alcohol value of 0.30 per cent, which was sufficient to explain the possibility of his having gone to sleep in the road. Dark clothing made it hard to see the sleeping form. The driver was released.

Medical Studies

While the primary function of the coroner's office is the *medicolegal* investigation of the deaths that fall within its jurisdiction, valuable *medical* benefits also accrue from the postmortem study of the pathologic material discovered at autopsy. The modern coroner should investigate 20 per cent of all deaths in a large community. His findings would comprise a variety of pathologic material not ordinarily available to the practicing hospital pathologist.

Sudden and unexpected death in infancy and childhood, a still incompletely solved problem, is an excellent example of a medicolegal question with strong medical overtones. The coroner's office can be the starting point for the pediatric pathologist who wishes to study this entity. An abundance of mechanical, thermal and electrical traumas is seen in the day-to-day work of the medicolegal office, as are details of the pathologic anatomy of chemical injury and poisoning. Figure 9 shows the appearance of the stomach of a child who died as the result of poisoning by ferrous sulfate. The presymptomatic and preclinical

stages of natural diseases, found incidentally in persons dying by violence, furnish a basis of understanding the etiology and pathogenesis of clinical states. These are a few of the situations in which the coroner's office can serve as a reservoir for research material leading to rational therapy for poorly understood diseases. Photography helps in recording and imparting this information.

Conclusions

It should be reiterated that the contemporary coroner's office is a multiphase institution. In its broadest concept, it functions as a public health office that utilizes knowledge acquired from the dead to make the community safer, healthier and more law-abiding. With the proper support of the medical, legal, editorial, governmental and lay segments of the community, it can render a unique service. Photography plays an essential part in the fulfillment of the many responsibilities that devolve on the modern medicolegal office in its day-to-day activity and its long-range planning.

Books

► THE DOCTOR IN PERSONAL INJURY CASES

By Harold A. Liebenson, member of Illinois, Chicago and American Bar Associations. 123 pages. 1956, The Year Book Publishers, Inc., Chicago. $4.00.

This brief document has been advanced to clarify some of the misunderstandings between the medical and legal professions with regard to personal injury cases. It is written by a trial attorney and as such expresses a primarily one-sided opinion. Not all of the difficulties that are encountered are due to the uncooperativeness of the medical profession as a good many trial attorneys would like to believe—and particularly are prone to convey to the unfortunate patient. While it is true that the great majority of physicians do not care to testify in court, the main reason for this attitude usually goes back to a disturbing experience with a poorly prepared or unscrupulous attorney. With few exceptions, medical men will not refuse to cooperate entirely with an outstanding attorney. This point is not emphasized.

The volume is small, is read easily, and may be of some help to the unexperienced medical witness. The importance of the physician in medicolegal medicine is emphasized with the author going so far as to state that "If the practitioner is so busy not to have time to fulfill the basic requirements in a personal injury case, it would be better to refuse to accept the patient." The chapter on medical reports is the most illuminating feature of the book.

E. H. O'P.

SYMPOSIUM

Trauma

RICHARD W. ZOLLINGER,[1] GEORGE J. CURRY[2] AND E. HARRY BOTTERELL[3]

RICHARD W. ZOLLINGER

GEORGE J. CURRY

E. HARRY BOTTERELL

DR. RICHARD W. ZOLLINGER (Moderator): Trauma now ranks fourth among the causes of death in the United States, preceded only by heart disease, cancer and vascular lesions of the central nervous system. Within the past year more than 36,000 persons died in traffic accidents alone, and some 1,250,000 persons were injured.

We will discuss the various phases of management of trauma, including first aid, transportation of injured persons, emergency-room measures and definitive treatment. Dr. Curry will begin by presenting his views on first-aid treatment at the scene of the accident.

DR. GEORGE J. CURRY: First I would like to substitute the term "immediate care" for the timeworn, out-of-date "first aid."

A very excellent article entitled "Let those crash victims lie," by Greer Williams, appeared in the August 20 (1955) issue of the *Saturday Evening Post*. It was written for the laity as well as for the medical profession. Dr. Botterell demonstrated the significance of that

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[2]Chief, Section for the Surgery of Trauma, Hurley Hospital, Flint, Michigan; Member, Board of Governors, American College of Surgeons; Chairman, Committee on Transportation of the Injured, American College of Surgeons.

[3]Associate Professor of Surgery (Neurosurgery), University of Toronto, Toronto, Ontario, Canada.

Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

article's title in his diagnostic clinic, describing very expertly the proper method for transporting a person with an injured back.*

In the group of people that surrounds a person injured in a traffic accident, there is always someone who feels he must do something. He may try to stand the injured person up, presuming if he can stand he is all right, or he rolls him over, wiggles a leg or an arm, and then asks if he is hurt. This is wrong.

It would be very helpful if some intelligent person at the scene would keep all such well-wishers in a circle around the victim until some well-trained person can arrange his being moved to an ambulance. My recommendation is to let an injured person alone until someone arrives who knows what to do.

DR. ZOLLINGER: Generally, the most serious traffic accidents occur in rural areas. Should a doctor ride in the ambulance sent to the scene?

DR. CURRY: I do not think doctors know too much about immediate care. It is better in the hands of a well-trained ambulance attendant or some other well-trained person.

DR. E. HARRY BOTTERELL: I do not know why you are maligning the rural districts. I sometimes go to football games, and I see some of the results of transportation in the city. I believe this is a problem for the police force and the ambulance services and the Red Cross, and it has to get down to that level in both city and country.

DR. CURRY: You mentioned football games. I am always amazed, when a player is injured and lying on the field, to see the trainer rush out, wiggle a leg or move an arm, or probably lean down and ask the player if he is hurt. Then they stand him up and walk him off the field amid great applause from 90,000 people. If the player can stand up and walk, apparently he is all right, irrespective of the possibility of a severe craniocerebral injury.

DR. ZOLLINGER: All right, whether it be urban or rural, do ambulances have properly trained attendants? Dr. Curry, you have done something about that problem in your town, Flint, Michigan. How do we go about making sure the men riding these ambulances are trained?

DR. CURRY: This is the responsibility of the medical profession in each community. It makes little difference whether it is done through an organized Committee on Trauma of the American College of Surgeons (as is the case in Flint), through a committee of the local county medical society or some other committee having to do with the hospital staff organization, so long as an educational program is established that will teach people who ride ambulances something about transporting an injured person.

DR. ZOLLINGER: Dr. Botterell, in your presentation this morning you spoke about transporting injured persons. Do you transport every injured person on his back?

DR. BOTTERELL: No. An unconscious person should be transported semiprone, that is, lying on his side, tilted over half onto his face, with a folded blanket or something under his head so that the jaw falls forward and the tongue falls forward and does not plug his larynx; any blood or secretions resulting from the injury will then trickle out the corner of his mouth. Those of you who are mouth breathers know that a little pool collects on the pillow if you sleep on your side, and this position is lifesaving in cases of injury where the patient is unconscious. I have seen many unconscious patients who were evacuated flat on their backs and arrived blue as your boot, and you know a damaged brain does not stand anoxia.

DR. ZOLLINGER: It is true, is it not, that many of these severely injured persons do not survive the transportation or die soon after they reach the emergency room? Do you think any of those patients could be saved?

DR. BOTTERELL: Yes, I do, particularly young adults. One never knows whether some of these patients arriving in the emergency room near death have been irretrievably damaged by the accident or whether it is the accident plus anoxia. Today some patients with serious head injuries are saved by performing tracheotomy at the appropriate moment.

DR. ZOLLINGER: You do not advocate that this procedure be done by somebody in the ambulance, though, do you?

*Botterell, E. H.: Fracture-dislocations of the thoracolumbar spine with spinal cord injury. Postgrad. Med. 20:177, 1956.

DR. BOTTERELL: No.

DR. ZOLLINGER: I want to discuss what should be done when the patient arrives at the hospital; we all agree we should position the patient to keep the airway clear during his trip to the hospital.

DR. BOTTERELL: That is basic.

DR. ZOLLINGER: After the injured person arrives at the hospital, would there be any argument about the following? First and most important, of course, we get that open airway; second, we splint obvious fractures, and third, we control obvious bleeding. Next we survey the patient rapidly and make notations for purposes of records. We start with the head and then go to the neck, chest, abdomen, symphysis, legs, perineum and back, and note the blood pressure, pulse and respiration. These things are fundamental and should be done at the immediate examination.

DR. BOTTERELL: You have forgotten the most important point. You have not recorded the level of consciousness.

DR. ZOLLINGER: The patient has multiple injuries.

DR. BOTTERELL: Yes, but you have charted his pulse, temperature and respiration, and that, I think, is one of the great fallacies. This is not just a head case. No patient who is regaining consciousness is getting worse as far as his brain is concerned; anyone whose unconsciousness is deepening is certainly getting worse. The level of consciousness is what counts in a head injury—not the pulse, temperature and respiration which everyone seems to emphasize. I want to know how conscious that patient was when he left the care of the last doctor.

I will tell you a story. One day in the County of Hampshire in England, a policeman came in and said, "You know, we picked up a fellow on the road, sir, and he was a'talkin' to me when I picked him up, but you know, he has gone unconscious." He had an extradural clot. One must chart the level of consciousness, write it down, include it in the work-up as one of the first things as far as the brain is concerned.

DR. ZOLLINGER: Also, probably, there should be some notation of previous medication.

DR. BOTTERELL: Certainly.

DR. ZOLLINGER: With all these multiple injuries, I think you will admit, Dr. Curry, that quite often the obvious injury—a badly deformed leg, for instance—is observed and treated while the patient dies from an injury in some other area such as the abdomen which is not so obvious. In these complicated cases of combined injuries, which condition would you treat first—say if the head, chest, abdomen and leg were injured?

DR. CURRY: In a case of multiple injuries there is always a person on the other end of the broken extremity. Obviously, a sucking wound of the chest takes first place. A chest full of blood or air takes priority. Injury to the abdomen in which there is a possibility of a ruptured spleen or liver or other part of its contents also takes first place, so far as saving the person's life is concerned.

A depressed skull fracture associated with a craniocerebral injury I do not think one can do anything about at the time except recognize it readily, of course, so that it can be handled by the type of talent present here.

Fractured extremities can be splinted so that they do not aggravate the more serious condition.

Therefore, one should take care of a chest injury or an abdominal injury first and the other injuries coincidentally, applying some type of splint to hold the fractured fragments in satisfactory position until the patient can be transported to the hospital.

I know the next question is going to be whether or not an ambulance attendant should know about a sucking wound of the chest. It is very likely the patient will be brought to the hospital with his wound sucking, and someone at the hospital will take care of that situation, unless the ambulance attendant is well trained.

DR. ZOLLINGER: What are you going to do about this chest wound?

DR. CURRY: Turn it over to a good thoracic surgeon or some other surgeon with appropriate knowledge, or, if this cannot be done immediately, I would put a piece of gauze over it and stop it from sucking. VASELINE® gauze is preferable.

DR. ZOLLINGER: How important is this chest injury?

DR. BOTTERELL: Vital—vital on its own account. Also, some of the common complications (and I use that term advisedly) of severe head injuries are pulmonary collapse, sometimes a tension pneumothorax, often a hemothorax, and interference with ventilation, and anoxia greatly aggravates the brain injury. We have seen patients brought in quite deeply unconscious who, when their pneumothorax (not even a sucking wound) was relieved by appropriate measures of aspiration or drainage or whatever, showed great improvement in level of consciousness. Note that I mentioned the level of consciousness again; that is the master word in following a head injury.

DR. CURRY: I would like to add, to those situations which take priority, a ruptured bladder. I think we forgot to mention severance of a major blood vessel, which certainly demands priority management.

DR. BOTTERELL: There is one situation which occurs in about 0.5 to 1.0 per cent of all cases of head injuries seen in a general hospital and which a general practitioner encounters about once or twice in his career. That is the classic extradural hematoma due to middle meningeal hemorrhage. Every year in our practice at our University center we encounter such a situation. A doctor telephones and says he has a patient who sustained a trivial head injury but his condition is worsening—one pupil is dilated and he is becoming more unconscious and so on—and he is an hour and a half's ride from anywhere. When such a patient is seen in the emergency department of a general hospital, an ill-informed resident may take him off to be x-rayed and investigated and maybe to fix his fracture, and there is no use doing that because that patient, who is going downhill rapidly, will be dead in an hour and a half.

DR. ZOLLINGER: How can you tell which head-injured patient is going to die, which should be observed, and which requires immediate surgery?

DR. BOTTERELL: The patient who is brought to the emergency room deeply unconscious, with damaged vital centers, irregular breathing and a rapid, thready pulse and without any other cause to account for his condition such as hemorrhage and the like, who has obstructed respiration no matter what position you put him in and in spite of the rubber airway in his mouth, represents a group in which the mortality rate is overwhelming. Usually they never recover consciousness; they die in the first 24 hours.

DR. CURRY: Dr. Botterell, do you diagnose the conditions you just mentioned as skull fractures or as craniocerebral injuries with or without skull fractures?

DR. BOTTERELL: Brain injury and complications.

The deeply unconscious patient who is not showing any recovery is the patient who dies, but when a patient has had a lucid interval and then rapidly goes downhill one must find out why. The doctor in an isolated community, once or twice in his lifetime, may be faced with making a hole in that patient's head and somehow letting the clot out. Dr. Rupert Rainey of Los Angeles has emphasized this. This applies, of course, to a very small group of patients who cannot be evacuated to a neurosurgeon or a general surgeon skilled in handling head injuries.

DR. CURRY: Then you believe every general practitioner should have a trephine available in his kit?

DR. BOTTERELL: Every hospital equipped to do an appendectomy should have a trephine. It may not be used more than once in five years, but when the need arises it should be available.

We had a case of manslaughter in Ontario when a hockey player crashed his opponent into the boards too hard and the boy got an extradural hematoma. He was 70 miles from anywhere and died en route to Toronto. The doctor must handle such a case with care and thought.

DR. ZOLLINGER: Getting back to the problem of the injured chest, we have placed Vaseline gauze on the wound and are going to get the lung expanded. Next we will get the blood out of the chest, and then worry about whether there is a ruptured hollow viscus. We are going to put a tube down the patient's throat

(you will not object to that, will you?) into his stomach; we will put an indwelling catheter in the bladder and check to see whether any blood is coming out. We may also put a little saline in and check the amount coming back to see if the bladder is injured. Are you going to object, then, no matter what this head condition is (the patient is not going to die from it), if we take him to surgery?

DR. BOTTERELL: No, subject to certain qualifications. I do not want the patient figuratively to be strangled. This is very important. One cannot submit a patient with a damaged brain to a general anesthetic that will involve any hypoxia or anoxia.

DR. ZOLLINGER: What anesthesia are you going to use?

DR. BOTTERELL: We want intratracheal tubes. The anesthetist has to do it to keep the patient properly oxygenated.

DR. ZOLLINGER: You have said that injuries to chest and abdomen take priority, but are there some exceptions in regard to injuries of an extremity?

DR. CURRY: Yes, a bad fracture-dislocation of an ankle, with the foot pushed up on the side of the leg and the danger that it may be lost, should be straightened. Severe fracture-dislocation of the elbow in which there is a hazard of forearm viability should be handled in the same manner.

DR. ZOLLINGER: Are you doing this in the emergency room?

DR. CURRY: One could do it almost anywhere—at the scene of the accident, in the ambulance or in the emergency department—but obviously it probably will not be done until the patient arrives in the hospital.

DR. ZOLLINGER: The majority of these injuries, particularly traffic injuries, involve the head, and I would like to ask Dr. Botterell about a problem which comes up in every emergency room. The youngest man, with the least training, usually is the man on service, and some fellow comes in on Saturday night, intoxicated, with small pupils and a hole in his head. Should he take up a bed? Or let us say he comes into your office; you cannot take him home with you. What are you going to do with this fellow if he goes out and gets a subdural hematoma in a couple of days? You are unjustly criticized, or are you? How are you going to know about this fellow?

DR. BOTTERELL: That is the most difficult question I know of. We have no more beds in our hospital than anyone else. If there is a bed anywhere in the hospital, we will admit a patient who has been unconscious—admit him for overnight. If no bed is available, he is held somewhere, somehow, and awakened every half-hour, primarily, and secondarily his pulse, temperature, respiration and blood pressure are checked. If there still is no space in the corridor or anywhere, he is sent home in charge of a relative who is instructed to awaken him every half-hour all night.

DR. ZOLLINGER: He has to have some pretty close friends.

DR. BOTTERELL: Most complications develop in the first 24 hours. If you get the patient through that period, nothing is going to happen so fast that circumstances will not permit getting him back to the hospital. We had three such cases in Toronto within about two weeks in various hospitals, and there was quite a fuss about it from the chief coroner, the press, and so on.

DR. ZOLLINGER: There is no absolute answer to it, is there?

DR. BOTTERELL: No.

DR. ZOLLINGER: How about the average scalp laceration? How would you handle it? Is it an office procedure?

DR. BOTTERELL: First, the scalp should be shaved for 2 in. around the laceration; most physicians neglect to do that. Secondly, every scalp laceration is a potential penetrating brain wound, because neither depression from the punching in of the skull nor actual laceration of the brain causes loss of consciousness in itself, so we feel that every scalp laceration should be palpated, using a sterile glove. The skull should be palpated with a sterile-gloved finger, not a probe which you would proceed to push through contaminated wounds into the brain.

DR. ZOLLINGER: Do you x-ray all of them?

DR. BOTTERELL: In our hospital we do, but obviously that is not always possible.

DR. ZOLLINGER: You will miss some, then.

DR. BOTTERELL: Not if one palpates the skull carefully. One may miss a linear fracture, but not a grossly depressed fracture very often unless it is very small.

DR. ZOLLINGER: Approximately one out of every 10 head-injured patients has some facial disfigurement. Dr. Curry, how do you handle facial injuries to get the best cosmetic result?

DR. CURRY: Facial lacerations should be properly sutured. I am sure everyone knows the wound edges should not be inverted or everted. The suturing should be meticulous. There is very little subcutaneous tissue in the face, and therefore débridement is unnecessary, in my opinion. Naturally, the wound should be thoroughly cleansed. We have had success with the fine silk sutures on little fine needles that come especially prepared for this purpose. We use interrupted sutures, and they should be placed very carefully—there is no need to hurry—and removed when the wounds are healed.

DR. ZOLLINGER: How soon do you take out the sutures?

DR. CURRY: When the wound is satisfactorily healed, usually within three to seven days. After that they become foreign bodies. Here again one must individualize according to the type of wound and the surgeon who sutured it.

DR. ZOLLINGER: I do not know whether I would leave them in much longer than four days at the maximum.

DR. CURRY: I do not think one can say we should leave them four days or five days or three days. We leave them until the wound looks healed and fixed—but I will go along with you if you say less than seven days.

DR. ZOLLINGER: You agree that in facial injuries one does not do extensive débridement.

DR. CURRY: Yes.

DR. BOTTERELL: Do you ever contemplate what happens to the floor of the anterior fossa when the face is pushed in?

DR. CURRY: That is difficult to answer. I think perhaps I would call in someone who knows much more about it than I do, but I might at least venture an opinion and perhaps, as you say, anticipate such a situation to be present. I would like to have someone else handle the situation *if* I thought he was capable of diagnosing it much better than I think I would be able to do. Is that what you mean?

DR. BOTTERELL: Donald Robertson, the plastic surgeon on our staff, has just reviewed about 20 cases of central fractures of the maxilla in which, unexpectedly, various evidences of compounding into the subarachnoid space were established, such as little collections of air around the base of the skull, leakage of spinal fluid when the patient was turned over, and so on. I think it is a point one should bear in mind in these head-on facial injuries.

DR. CURRY: I would like to delete forever the word "compound" from our descriptive terminology in cases of fracture. Webster defines it as many things, but I have never been able to associate the word with a fracture. I do not know what a compound injury is unless it is a piled-up injury. I would like to substitute the word "open."

DR. ZOLLINGER: Getting back to this original injury, there is a severely injured abdomen or chest, as we said. We are going to splint the fractured extremity and are not worrying about the head if we get intratracheal anesthesia, but this patient is quite badly cut up about the face and may have antral fractures, fractures of the zygoma or mandible. What are you going to do about those at the time you take out a spleen?

DR. CURRY: I do not think I would worry about them at the time I was taking out a spleen. That type of fracture could wait. Some bone fractures should not wait. The ones you mentioned are of flat bones, and one could wait until a good oral surgeon could correct the deformity.

DR. ZOLLINGER: How long could one wait? We get the spleen out—

DR. CURRY: You have it mixed up with the fractured spleen for which splenectomy has been done. I think when the patient is in satisfactory condition following splenectomy one could proceed.

DR. BOTTERELL: Is it not a matter of degree? If a patient has a floating maxilla and fractured mandible, he is going to have some trouble breathing if you take out that tube.

DR. CURRY: I will still stick to my first state-

ment, that even though it is floating it still should be in the hands of someone who knows how to care for it; and I think there are a few of us left who would have sense enough perhaps to immobilize that situation temporarily so that the patient could breathe.

DR. ZOLLINGER: Dr. Botterell, when should one x-ray the head? How much of an emergency is it?

DR. BOTTERELL: It is not an emergency at all, really, unless one is looking for a com—, well, one of those fractures that opens from the outside to the inside, and the brain is coming out on the scalp, or some spinal fluid is coming out of the corner of the scalp wound, or one feels a penetrating wound through the skull. Certainly we feel those patients should be fully assessed at the first possible opportunity.

DR. ZOLLINGER: What is the use of x-ray, then, when you know the brain is injured?

DR. BOTTERELL: It guides you as to how many in-driven bone fragments there are, how far they go, and so on. Actually, there are relatively few occasions to x-ray a skull as truly an emergency measure.

DR. ZOLLINGER: How about an extremity? How important is it to get an x-ray right away?

DR. CURRY: Quite important.

DR. ZOLLINGER: Are you going to let the bleeding spleen go?

DR. CURRY: I do not think making an x-ray with a portable machine is going to interfere with a bleeding spleen.

DR. ZOLLINGER: Your portables must be better than ours.

You said a while ago we could splint the extremity and take the patient upstairs and you were not going to bother about him at all.

DR. CURRY: The patient is in the hospital now, is he not?

DR. ZOLLINGER: Yes.

DR. CURRY: I see no harm in taking a portable of the suspected fracture area.

DR. ZOLLINGER: Let us take up the problem of shock. We are going to give the patient replacement therapy—some fluid expander, perhaps plasma, albumin or something until blood is available. How long should you observe a patient in shock before giving him definitive therapy?

DR. CURRY: Not very long.

DR. ZOLLINGER: You have seen, as I have, that some patients are given 5 or 10 pints, and, goodness, it goes on forever. Would you argue that you should get in the first two pints, for example, if the pressure is down, in the first 10 or 15 minutes if possible and that you should not wait more than, let us say, 2000 cc. before moving the patient or doing something definitive?

DR. CURRY: No, but in all good hospitals one ought to have some means of determining blood volume. If not, then one must use good horse sense.

DR. ZOLLINGER: How do you make this blood-volume determination?

DR. CURRY: That is placed in the hands of persons who have very special talents.

DR. ZOLLINGER: Do you use hematocrit or blood count or do real blood volumes?

DR. CURRY: The latter, in a good hospital.

DR. ZOLLINGER: Evans blue dye and all that?

DR. CURRY: I think you can give it to them beforehand.

DR. ZOLLINGER: You are going on the blood count and physical findings.

DR. CURRY: They are very helpful.

DR. ZOLLINGER: How about overloading the patient's head with too much fluid if you are worried about a head injury?

DR. BOTTERELL: If a patient is in shock one should not pay any attention to that.

DR. ZOLLINGER: How are you going to handle an unconscious patient following a head injury?

DR. BOTTERELL: We have outlined it fairly well. We have established a base line of his level of consciousness; he can move his arms and legs; we know what his reflexes show; we look at his pupils, and see if any spinal fluid or blood is coming out of his ears or nose or trickling down his pharynx; then you have a base line on which to proceed. If consciousness is returning, you nurse him along, insuring that his airway is clear.

DR. ZOLLINGER: Let us say the patient has a relatively lucid interval and then suddenly becomes unconscious. What conditions or le-

sions will cause this type of situation?

DR. BOTTERELL: This is the vital point in managing complicated brain injuries. The extradural hematoma is the classic one, and perhaps the least common, and in the trivial head injury it is post-traumatic meningitis. There could be a crack in the region of the accessory nasal sinuses and the communication with the subarachnoid space in the absence of any serious loss of consciousness. So post-traumatic meningitis produces loss of consciousness after a lucid interval, and a collection of air inside the head, pneumocephalus, can take up so much room in the subdural space it makes the patient unconscious or drowsy and confused. Finally, intracerebral clots, and, in the more severe head injuries, an acute subdural hematoma, will do the same thing. A list which pretty well covers the situation is: extradural and subdural clots and post-traumatic meningitis and pneumocephalus.

DR. ZOLLINGER: Have you any choice of sedatives?

DR. BOTTERELL: We try to use agents that do not depress cough reflex or the respiratory center. By and large we use LUMINAL® sodium or paraldehyde.

DR ZOLLINGER: The great majority of injured patients who are admitted to the hospital have some form of fracture. Dr. Curry, which fractures would you treat by closed reduction?

DR. CURRY: All fractures in children should be manipulated, reduced and fixed appropriately in plaster. I do not think we should worry about overriding. In fact, there are those who say a side-to-side apposition is better than an end-on, because of the hazard of absorption in the latter. I should point out that one has to be more or less resilient in defining a patient as a child. A child is someone up to, let us say, 10, 11 or even 12 years of age. When speaking of both sexes one should consider children as being slightly under the age of adolescence.

In adults, when satisfactory alignment is obtained and maintained, we can make a general statement that perhaps many fractures may be handled by closed reduction.

All of you have taken care of fractures of the distal end of the radius which are commonly called Colles' fractures. These should be handled by manipulation, reduction and fixation in plaster of paris or some other type of splint fixation. A moderate degree of offsetting is, I think, acceptable, but I believe a broken bone should be replaced as nearly as possible to its normal position. Then again, we should do something about fracture fixation that will place the neighboring joints in a mobility potential. This problem was excellently described by Dr. Scuderi.* He outlined the fractures which can be handled by manipulation, by traction and by open reduction and stated the indications properly and very well.

DR. ZOLLINGER: Which ones would you handle by traction?

DR. CURRY: A good example would be a severely comminuted fracture of the trochanterian area of the femur, which does not lend itself to the insertion of any type of metallic appliance; this should be placed in traction. The same is true in fractures of the lower end of the femur in which there is a multiplicity of fragments; these do not lend themselves to a fracture assembly and internal fixation.

DR. BOTTERELL: Dr. Curry, perhaps you could help me with some of the patients I see. Let us say a man is unconscious and you think an operation on the head is necessary. He has a fracture of the femur, and you tie him up in traction, and it is very complicated to move him to an operating room. Do you ever use something more than a Thomas splint for that type of case? Have you ever used a Tobruk-Thomas combination?

DR. CURRY: We have had that situation arise. I do not quite know how to answer it. The craniocerebral damage and associated osseous injury apparently are taking first place, and he still has the fractured femur. I think I stated at the onset that perhaps the extremity could be disregarded but splinted for the time being until the operation on the head has been taken care of.

DR. BOTTERELL: The patient may be very

*Scuderi, Carlo: Both-bone fractures of the leg. Postgrad. Med. See p. 407, this issue.

restless and thrashing around for several days.

DR. CURRY: You want to move him to the operating room and do the head surgery?

DR. BOTTERELL: You have to, yes.

DR. CURRY: I think you can extemporize with some type of apparatus, or put him in a Thomas splint with the traction that previously was attached to the bed, attached to the splint. It can be done. We have done it any number of times. Sometimes you can bring the neurosurgeon to the patient and perform the operation with the patient in his bed. Has this happened in your hospital?

DR. BOTTERELL: Not if I can help it.

DR. ZOLLINGER: Which fractures do you handle by open reduction?

DR. CURRY: Before answering, I would like to say that severe supracondylar fractures of the humerus should, I think, be placed in traction. Perhaps I might add to that the severe open fracture in which there has been marked comminution of fragments and destruction of skin and adjacent muscle, where you would like to keep the wound under observation.

To answer your question about open reduction, this is mandatory in certain fractures, including a fractured hip in an elderly person. This fracture demands open reduction—whether it is a fracture of the femoral neck or of the intertrochanteric area—because in this situation we are not only treating the fracture and making an elderly person more comfortable but we are also treating hypostasis. I am sure you all appreciate that the death rate from hip fractures has fallen greatly since this philosophy has been adopted. First we have the saving of life, which is mandatory; then the saving of the limb.

I mentioned the fracture-dislocation of the ankle in which the foot is blue, and the fracture-dislocation of the elbow in which there is a danger of impaired forearm function.

Then we have operations of choice. In the situations I just mentioned, open reduction could be called a procedure of necessity. Dr. Scuderi mentioned the oblique fracture of the tibia associated with fracture of the fibula, which is notorious in that it slips. That, to me, is an indication for open reduction as a matter of choice and necessity. Then there are open reductions of fractured patellae in which there is wide separation of fragments, primarily opened and apposed or removed; fractures of the olecranon in which there is wide separation, those in which you know and you feel there is interposed tissue, and those in which the fractures are irreducible by any means at your disposal.

I do not like to subscribe to many manipulations of fractures. They are secondary insults to an already injured structure. If a reasonably good attempt at reduction fails, and you are not satisfied with the position of fragments, I would accept it as a case for open reduction. We have to guide ourselves by adopting certain principles and still individualize the situation.

I think you can recognize the illustration in figure 1 as an extensive supracondylar fracture with wide separation of the fragments. The traction in this case had to be supplemented by the use of a screw on one side (figure 2), because of continuous slippage of the distal segment. A Kirschner wire was placed through the olecranon. Figure 3 is a photograph of the little girl who sustained this fracture, and shows the type of olecranon traction we have used very successfully since 1941 for supracondylar fractures with wide displacement of fragments. The patients are very comfortable, and the method has the added advantage of elevating the extremity and doing away with the danger of a Volkmann contracture; it certainly is an aid to circulation. The little girl obtained full function as far as her carrying angle is concerned (figure 4). Figure 5 shows that she has complete flexion of the elbow.

Another supracondylar fracture, the flexion type, is shown in figure 6. There was marked displacement (figure 7). The patient was a 70 year old woman. With the type of management I just described, there was satisfactory apposition of the fragments (figure 8).

Figure 9 illustrates a Volkmann contracture, one of the most horrible deformities that can occur. If we can do anything to avert this situation, we should do it.

A fracture of the surgical neck of the humerus with marked displacement of fragments

FIGURE 1. Comminuted supracondylar fracture of right humerus with marked displacement.

FIGURE 2. Same case as figure 1. Manipulation, open reduction, overhead olecranon traction and supplementary screw fixation to prevent displacement of distal segment were employed.

FIGURE 3. Overhead olecranon traction.

is shown on the left in figure 10. The right-hand side shows the appearance with the upper extremity placed in traction. There is satisfactory reduction, and this has been verified by a lateral film.

Figure 11 illustrates what happened in a fracture-dislocation of an ankle when the doctor waited for the swelling to go down before doing anything. While he waited, the swell-

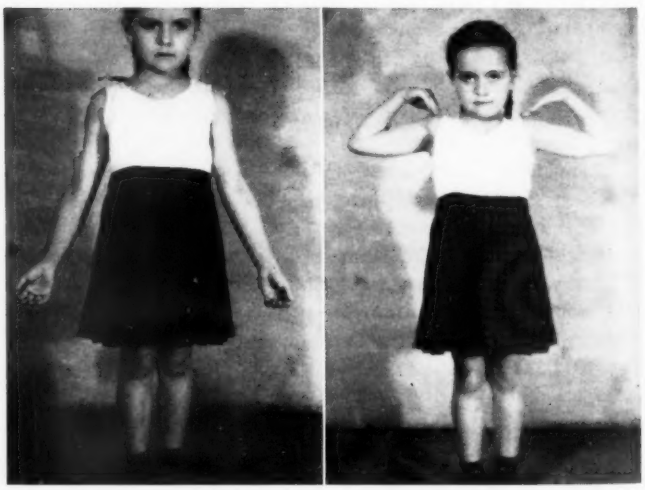

FIGURE 4 *(left)*. Appearance after three months. Extension is complete; the carrying angle of the right elbow is normal.

FIGURE 5 *(right)*. Complete flexion of right elbow.

FIGURE 6. Comminuted supracondylar fracture of right humerus, with anterior displacement of the elbow. Patient was a 70 year old woman.

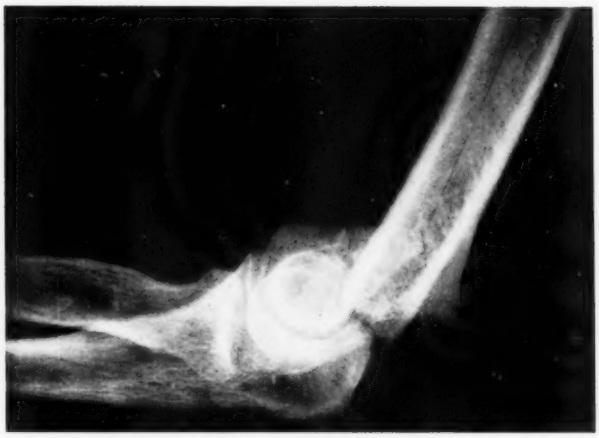

FIGURE 7. Lateral view of same case.

ing increased, many blebs formed, and a very difficult situation followed. This fracture should have been handled within the first hour after it happened. There are certain fractures that are measured in terms of minutes; others are measured in terms of seconds, and some few in terms of hours. I would like to impress you with this photograph because reduction is extremely difficult after a situation such as this has developed.

FIGURE 8. Elbow in satisfactory position after reduction and overhead olecranon traction.

Do it now! That would be a summary for the illustrations I have described. Fractures should be handled *now*, they should be reduced *now*, except when the associated circumstances prevail that have been discussed here so well by Dr. Botterell and Dr. Zollinger —complicating multiple injuries.

DR. ZOLLINGER: We have a few questions from the audience. Dr. Botterell, here is one: "You did not mention the importance of a blood pressure estimation at the earliest possible moment and a recheck periodically. Do you consider this advisable?

DR. BOTTERELL: Yes, and one should also gauge the respirations and their rhythmicity or periodicity, and the pulse rate. It is well established that an increasing intracranial space-occupying lesion in the face of normally functioning vital centers causes a rise in blood pressure and a slowing pulse. However, after a good, brisk head injury with the force transmitted to the brain stem, as it so often is, the vital centers do not always respond normally. The finding of a rise in blood pressure and a slowing pulse is very valuable, but if it is absent it should not cause you to disregard the significance of an intracranial lesion manifested by increasing depth of coma.

I should add also that the patient may die

FIGURE 9. Volkmann's deformity.

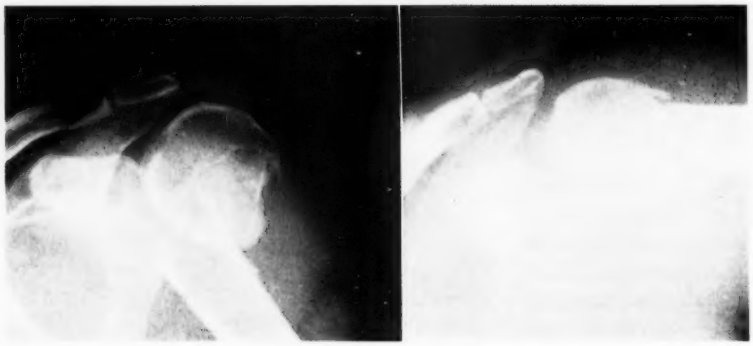

FIGURE 10. Comminuted fracture of the surgical neck of the left humerus. Reduction by lateral skin traction.

of an acutely expanding intracranial lesion without any evidence of papilledema in the optic nerve heads.

DR. ZOLLINGER: "At what level of shock or consciousness would you let chest or abdominal work proceed?" I think Dr. Botterell answered that. If you have a patient with a widely dilated pupil and obvious spasticity with a poor prognosis, there is no use doing anything. Would you agree to that?

DR. BOTTERELL: Yes.

DR. ZOLLINGER: If the head injury is such that it can be observed and the patient does not respond after three or four pints of blood have been administered, then there may be severe damage in the intra-abdominal cavity or the chest and we should proceed. I do not think the state of shock or consciousness would have much to do with the chest or abdominal work. Would you agree with that?

FIGURE 11. Edema and pronounced bleb formation in case of fracture-dislocation of right ankle. Photograph was taken five days after injury. Early reduction would have prevented this condition.

DR. BOTTERELL: Yes.

DR. ZOLLINGER: Here is a question I think you have answered. "What about tracheotomy in head injuries?"

DR. BOTTERELL: It is a lifesaving measure in appropriate cases when a clear airway cannot be established either by positioning or by an ordinary rubber airway.

DR. CURRY: We have a policy in our hospital that the time to do a tracheotomy is when you think of it.

DR. BOTTERELL: We also quote that same statement.

DR. ZOLLINGER: Someone said to me that you could get by sometimes, if you did not have the nerve to do a tracheotomy, if you pushed a couple of No. 13 needles into the trachea—that this might work until you got to someone who could do a tracheotomy. Do you think that might suffice?

DR. BOTTERELL: There is a better substitute than that. It is much better to put an intratracheal tube down and leave it down until you can get the patient wherever you are taking him. Our anesthetists were very shocked by that, but we had occasion to observe two or three patients who had had intratracheal tubes in place for two or three days. They did not seem to produce any ill effects. When we took out the tube the larynx worked all right. I do not recommend this measure, because the tube coats up with secretions inside and the lumen quickly becomes too narrow, but if one must evacuate or transport a patient who, one thinks, needs tracheotomy and the setting is unsatisfactory and a tube is unavailable, I would sooner see an intratracheal tube put down.

DR. ZOLLINGER: What about lumbar puncture in the unconscious patient?

DR. BOTTERELL: We do not employ lumbar puncture routinely at all. We utilize it in attempting to diagnose post-traumatic meningitis, and from time to time perhaps to relieve headache when the patient is steadily regaining consciousness and we think he has a sticky, yellow, dirty spinal fluid. I do not believe lumbar puncture should be done with impunity, that is, just casually. It should be done only when definitely indicated.

Books Received

New books received are acknowledged each month. As space permits, books of principal interest to our readers will be reviewed more extensively. Reviews will be found in this issue starting on page A-130 and additional listings on pages 348, 379 and A-138.

Culture and Mental Disorders. By Ralph Linton, Sterling Professor of Anthropology, Yale University, New Haven, Connecticut, and edited by George Devereux, Director of Research, Devereux Foundation, Devon, Pennsylvania. 139 pages. 1956, Charles C Thomas, Springfield, Illinois. $4.50.

Progress in Hematology. Volume I. Edited by Leandro M. Tocantins, M.D., with 27 contributors. 336 pages, illustrated. 1956, Grune & Stratton, Inc., New York and London. $9.75.

Cytology of the Blood and Blood-forming Organs. By Marcel Bessis, Director of Research Laboratory, Centre National de Transfusion Sanguine, Paris, France. Translated by Eric Ponder, Nassau Hospital, Mineola, New York. 629 pages with 405 figures and 22 color plates. 1956, Grune & Stratton, Inc., New York and London. $22.00.

Biochemistry of the Eye. By Antoinette Pirie, Ph.D., Margaret Ogilvie's Reader in Ophthalmology, and Ruth Van Heyningen, D. Phil., staff member, Nuffield Laboratory of Ophthalmology, Oxford University, England. 323 pages, illustrated. 1956, Charles C Thomas, Springfield, Illinois. $7.00.

The Spine; Anatomicoradiographic Studies; Development and the Cervical Region. By Lee A. Hadley, M.D., Senior Attending Roentgenologist, Syracuse Memorial Hospital, and Clinical Associate Professor of Public Health, New York State College of Medicine, Syracuse. 156 pages, illustrated. 1956, Charles C Thomas, Springfield, Illinois. $6.50.

Emotional Hazards in Animals and Man. By Howard S. Liddell, Ph.D., Professor of Psychobiology and Director, Behavior Farm Laboratory, Cornell University, Ithaca, New York. A monograph in American Lectures in Objective Psychiatry. 97 pages. 1956, Charles C Thomas, Springfield, Illinois. $2.50.

First MEDICAL EDUCATION AWARD Winners

at 26th Annual Meeting of the

Biological Photographic Association

Supported by a grant from POSTGRADUATE MEDICINE, the BPA Medical Education Award was established this year to encourage medical photographers to improve the teaching content of their photographs. The competition and showing were held in conjunction with the annual meeting of the BPA at Rochester, New York, during the week of August 26.

The exhibition judges awarded the cash prizes to the winning entries in each of five categories: monochrome prints, color prints, transparencies, motion pictures and special displays.

Reproduced here are the award-winning photographs in the first three categories. First place in the motion picture division went to Dr. David S. Ruhe, University of Kansas Medical Center, Kansas City, Kansas, and the prize for the best special display to Luther R. Gilliam, Veterans Hospital, Brooklyn, New York.

The Medical Education Award will be an annual feature of the BPA meetings.

Monochrome print: Thoracic aortic aneurysm and repair
Gene K. Davis, The Methodist Hospital, Houston, Texas

Color print: Hypermature cataract. Lens delivered spontaneously through a corneal perforation due to *Pseudomonas aeruginosa*
Charles M. Bailey, St. Mary's Hospital, Rochester, New York

Transparency: Finger—chondrosarcoma
Martha M. Brunings, Rochester General Hospital, Rochester, New York

CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital
Hines, Illinois

Case Report

A 38 year old white man, a farmer, was well until one year before admission to this hospital when he complained of abdominal discomfort. About six months later, he began to experience loss of appetite, nausea and vomiting, and a full feeling after eating small amounts of food. About that time, he also began noticing progressive weakness and low back pain aggravated by activity. Three months later, in September, he first noticed a nodular swelling in the right groin. Similar involvement of both groins, axillae, elbows and neck followed shortly. These nodes grew to 3 and 4 cm. in diameter and were hard and somewhat painful. In October, his weakness and pain became progressively worse and intermittent fever developed. He was forced to quit working and entered a private hospital where he was treated with penicillin for rabbit fever. However, his condition continued to grow worse. Intermittent frontal headaches, not relieved by aspirin, and lasting about one to two hours, began occurring daily along with insomnia.

In December, he was hospitalized elsewhere where a diagnosis of Hodgkin's disease, sarcomatous type, was established from biopsy of a submaxillary node. The patient was sent to Hines Veterans Administration Hospital on January 1. During the next six months he lost about 40 lb. in weight (from 190 to 150 lb.). During the last month he complained of hot flushes of the face and mouth, usually referred down both arms.

Past history—Childhood illnesses included scarlet fever and diphtheria. The patient had been discharged from the army after two years' service because of nervousness.

Physical examination—The patient was a well-developed, somewhat undernourished and emaciated 38 year old white man, who was sweating profusely about the head and neck. Blood pressure was 120/70, pulse rate 90, temperature 99.2° F. Bilateral submaxillary masses were matted together and about 3.5 cm. in diameter. The lungs revealed diminished diaphragmatic excursions with questionable dullness at both bases. The abdomen was somewhat distended and a hard nodular fixed mass filled the epigastrium. Several question-

able smaller nodular masses were noted in the lower abdomen. Tenderness to percussion was present over the thoracic and lumbar spine. Evidence of marked weight loss was present in all extremities. (Bilateral axillary adenopathy, 1 to 2 cm. in diameter, and bilateral enlarged epitrochlear nodes were also prominent. These nodes were slightly tender and fixed to underlying tissues.) Remainder of physical examination was essentially negative.

Laboratory findings—On admission, January 1, the red blood cell count was 4,050,000, white blood cell count 5800, and hemoglobin 12 gm. Serologic tests were negative. Urine was acid with a specific gravity of 1.020 and no albumin or sugar. Microscopic examination disclosed a few white blood cells. Roentgenogram of the chest revealed widening of hilar shadows and residuals of pleurisy at both bases. A flat plate of abdomen revealed no demonstrable pathology.

An electrocardiogram made on January 4 showed sinus rhythm with ventricular premature contractions and was interpreted as probably normal.

On January 5, the nonprotein nitrogen was 39.5, serum albumin 2.4, globulin 2.2, and sodium retention rate 2 mm. The red blood cell count was 4,400,000, white blood cell count 7600, hemoglobin 12 gm., polymorphonuclear cells 88, lymphocytes 11 and eosinophils 1.

A gastrointestinal series on January 6 showed marked thickening of the mucosal pattern of the stomach. The distal end of the stomach and duodenal bulb were displaced anteriorly, superiorly and toward the midline by what appeared to be an extrinsic mass. The distal part of the stomach wall was normally pliable and barium passed immediately through to the duodenum. The duodenal bulb was irregular but did exhibit irritability. The duodenal sweep was normal. There was a moderate amount of barium residue at the end of five hours.

On January 14, the red blood cell count was 4,560,000, white blood cell count 3500, hemoglobin 13 gm., myelocytes 2, juveniles 2, bands 18, segments 70, lymphocytes 6, monocytes 2. Later the red blood cell count was 4,900,000, white blood cell count 6600 and hemoglobin 14.5 gm.

On January 18, the red blood cell count was 4,100,000, white blood cell count 4300 and hemoglobin 12 gm. Hematocrit was 43, nonprotein nitrogen 73.5 mg. per cent, sodium chloride 598 mg. per cent, carbon dioxide 33 per cent.

Hospital course—The patient was given a regular diet, along with tincture of belladonna, 15 drops four times daily, and AMPHOJEL®, analgesics and mild sedation, as required. Slides from submaxillary node biopsy prepared elsewhere were reviewed by the pathology department here and diagnosed as reticulum cell sarcoma. The patient was presented to the lymphoma board on January 7, when a course of nitrogen mustard therapy was recommended. Daily temperatures rose to 99.2° to 99.8° F., pulse rate varied between 76 and 106, and respirations were about 20. On January 10, nitrogen mustard, 6.8 mg., was given intravenously and repeated for two days.

At 11:00 P.M. on January 12 the patient complained of severe pain in his left shoulder and generalized abdominal discomfort. On the following morning he continued to complain of abdominal pain with tenderness most marked in the upper abdomen. Rebound tenderness was present in both upper and lower abdomen. Bowel sounds were absent and the patient had neither moved his bowels nor passed gas by rectum. Blood pressure fell to 86/50, temperature varied from 97° to 99° F., pulse rate climbed from 96 to 116, and respiration showed gradual increase. A flat plate of the abdomen showed air under the diaphragm. Penicillin, 100,000 units every two hours, and streptomycin, 5 gm. every four hours, were administered intramuscularly along with Wangensteen suction and a 2000 cc. transfusion of whole blood. The blood pressure rose to 115/80, the pulse rate rose to 150, respirations became rapid, and the temperature rose to 101.2° F. It was decided on January 13 that the patient could not tolerate surgery. Treatment with penicillin, streptomycin, Wangensteen suction and intravenous administration of fluids, 4000 to 5000 cc. daily, was continued. The patient's condition continued to

grow worse steadily and he became intermittently delirious.

The abdomen became less tender, but continued to be distended. The pulse and respirations remained rapid and the temperature remained around 102° F. On the evening of January 18, he lapsed into a state of coma from which he did not recover; he died at 2:35 P.M. on January 19.

Discussion

DR. COSTICH: The treatment of this patient produced some unusual results and we have Dr. LeRoy here to discuss the case.

DR. LEROY: This case presents several points which I think merit discussion. The first point is the relatively short course and relatively rapid progression of the symptomatology of the disease, reticulum cell sarcoma. Starting from the onset illness in June to the patient's rather desperate condition by the time he arrived here in December, I think it is of interest that initially he had loss of appetite and symptoms were related to the gastrointestinal tract, because this is not the usual mode of onset of the lymphomas. It would suggest, in retrospect, that involvement of the gastric tissues by the lymphoma was apparently commencing or was already in existence at the time of his initial ill health. The rapidity with which the obvious lymph nodes grew is not very significant and would not permit any definite conclusions.

By the time he arrived here in December the clinical picture was well established. He was febrile and rather considerably deteriorated. He had a general enlargement of all the lymph nodes which could be palpated. It is noteworthy that the record states that he had enlarged epitrochlear nodes. Sturgis makes the point in his book on hematology that epitrochlear nodes are seldom involved in Hodgkin's disease and that they are quite usual in lymphosarcoma. Without saying that it is a positive differential feature, it is a point of some interest. It is also of interest in trying to estimate prognosis, because the usual course of lymphosarcoma is much more rapid than that of Hodgkin's disease. This man had remarkable tumors in his upper abdomen which were easily visible and easily palpable and, as could be seen on x-ray examination, he had changes in his stomach.

Involvement of the gastrointestinal tract by lymphomas is not uncommon. Generally it tends to be multiple, occurring throughout the bowel in one place or another. The available literature on gastrointestinal involvement is highly confusing, because one author will say that in Hodgkin's disease multiple ulcerations occur, and another author will say that in the same disease large infiltrations occur. The simple fact is that infiltration which may result in ulceration or in obstructive phenomena is not uncommon in these diseases. Complete intestinal obstruction is unusual. We have seen apparently complete obstruction on two occasions in this hospital in the past two years. The order of frequency of gastrointestinal tract involvement by this group of diseases is given as: stomach, jejunum, ileum, colon and rectum. The causes of death are rather generally stated to be cachexia from faulty nutrition, perforation and, rarely, hemorrhage from the so-called sarcomas of the stomach; lymphosarcoma and reticulum cell sarcoma comprise over half the types seen.

This patient had never had any specific therapy, and the question was what form of treatment we should use. In trying to decide between the available forms of treatment, namely, roentgen therapy and treatment with nitrogen mustard, we have no very hard and fast defensible criteria by which to operate. The experience most of us have had with x-ray, of course, covers a rather long period of time. The obvious disadvantage of x-ray is that, with a widespread disease of the type this patient had, it is quite difficult to treat all the involved areas simultaneously or even very quickly. Here we had a very uncomfortable patient and we wanted to relieve the discomfort as much as possible.

With x-ray therapy there is a definite time factor. You can treat one or two portals a day, and, although you can relieve some patients in this way, you cannot do it with the speed that appears to be desirable under the circumstances. Nitrogen mustard, however, gives one the opportunity of treating the entire patho-

logic process very quickly. Many contemporary authorities on Hodgkin's disease speak of "detoxifying" patients by administering nitrogen mustard, thus getting a rapid course of therapy to all of the affected tissue, with rather prompt subsidence of symptoms. In the usual context, the symptoms to be detoxified are the fever and the extreme cachexia.

In trying to determine which form of therapy to use, it is desirable to try to assess the stage of the disease. Is the patient almost terminal, or does he present simply a large number of easily palpable and visible tumors, but with vital structures and reserve strength not compromised to any extent? In Hodgkin's disease in particular this is very difficult to determine. All of us have seen patients with Hodgkin's disease who have had Pel-Ebstein fever for several months, who are emaciated, who have large lymph nodes, who have varying amounts of anemia, and who have spectacular remissions from radiation therapy. On the other hand, we have also seen patients with disease of rather short duration and in whom the lymphadenopathy is not particularly spectacular, but who deteriorate very rapidly under treatment, and die quickly.

Did we have any clues in this case to tell us whether or not the disease was far along? We did have a couple of clues. One clue is in the blood counts. In Hodgkin's disease the blood picture is nonspecific throughout most of the course of the disease. As it goes into the terminal phase lymphopenia is a constant finding; so that, when you see patients with Hodgkin's disease with only 4 or 6 per cent lymphocytes, or when the absolute number of lymphocytes is very small, as it was in this patient, you are entitled to think that the process is approaching the final stages. The reason for the lymphopenia apparently is that lymphopoietic tissues are ultimately almost entirely replaced by the granuloma, so they are no longer a source of lymphocytes. Presumably, if a patient could survive the other dangers of Hodgkin's disease, he would reach a stage where he would not produce any lymphocytes at all because of the conversion of all the lymphoid tissue into sclerotic granulation tissue. Another feature which is seen in the terminal stage of Hodgkin's disease, and also of lymphosarcoma, is an alteration of the plasma proteins. The plasma protein values for this patient were quite reduced.

The albumin was 2.4 gm. and the globulin was 2.2 gm. In a number of patients, particularly those who have edema, we have obtained some rather startlingly low values. We have had patients whose total plasma proteins were 3 gm. and one who went down to as low as 2.7 gm. The literature on the subject is quite variable, presumably because patients have been studied at all stages of the disease. While a patient is in fair health and has an adequate reserve of lymphoid and hemopoietic tissue, the plasma proteins remain at fairly normal levels, but as the terminal stage is approached, the plasma proteins get lower. I think one should consider that in the absence of any other adequate cause, a patient with seriously depleted plasma protein is in the terminal or certainly the preterminal stages of lymphosarcoma or Hodgkin's disease.

It is quite interesting to speculate, if I may, on why the proteins are so depleted. Those patients often have extremely little involvement of the liver, and it is of some interest that those low values occur in conditions associated with a reduction of the lymphocytes and alteration of the lymphopoietic tissue. This leads one to wonder about some of the studies of Sabin and others from the Rockefeller Institute concerning the formation of proteins by lymphocytes. These workers believe that formation of proteins is one of the main functions of lymphocytes.

Anyway, we felt that this patient could not tolerate x-ray therapy. Because of the general involvement, and particularly because of extensive gastrointestinal tract involvement, we thought it would be better to give him nitrogen mustard. We could have used x-ray therapy and, in retrospect, I think it is possible he would have survived. With nitrogen mustard, however, shortly after he received the third dose, perforation of the stomach occurred. We might have anticipated this from certain data which are available. Studies of lymphoma tissue treated with nitrogen mustard have shown that there is amazingly rapid necrosis and

deterioration of the tumor tissue—in a matter of hours after administration of the drug. It is obvious that if the tumor tissue is only in lymph nodes and if one caused them to undergo a rather rapid necrosis, there is no great disadvantage. But if there is sudden necrosis of tumor which is in contact with gastric juice, there is the prospect of rapid digestion of nonviable tissue. There is thus very good reason to suspect what we did not suspect in this case, that peptic perforation could occur. I think this is probably the simplest and easiest way to visualize the course of events in this patient.

One asks then: Would this have happened with radiation therapy? I think it is less likely, since one would probably not attempt to deliver radiation so vigorously that necrosis would occur. In case of an extensive gastric tumor, such as this man had, roentgen necrosis would make the tumor just as liable to peptic digestion as the nitrogen mustard did.

So we had a situation where the rapid changes which nitrogen mustard produces in tumor tissue affected this man's gastric tumors to the extent that they could be digested and could perforate.

The problems that arose with respect to the management of this patient after perforation occurred were of considerable interest. Our first feeling was that this man was in such a desperately poor condition that any attempt at surgical intervention would be fatal. We thought that perhaps—and I must say we had no experience to back this up—the patient might be carried along by conservative measures, with penicillin and sulfadiazine and other antibiotic agents, plus gastric suction and general supportive measures. The surgical consultants were of quite the opposite opinion. They felt very strongly that there was no help for a patient with a perforated stomach unless surgery was performed. Within the next two or three hours, while the patient was being transfused and prepared for surgery, his general condition deteriorated so much that the surgeons decided not to operate. The patient was obviously in such poor condition that we felt entitled to chance his recovering with conservative treatment. Unfortunately, he did not.

In conclusion, then, we have discussed a patient with lymphoma with gastric involvement which was quite extensive. Within a very few days after administration of nitrogen mustard therapy spontaneous perforation of the stomach occurred.

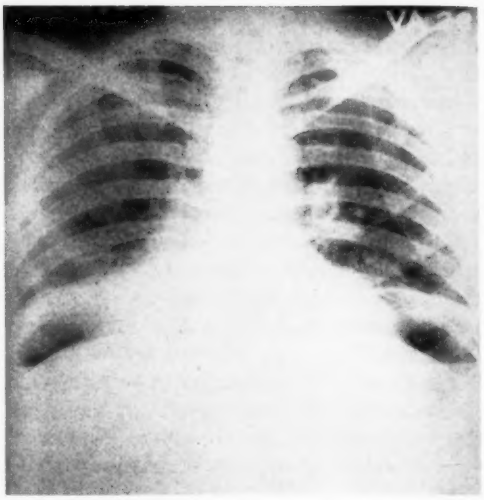

FIGURE 1. Roentgenogram of chest showing hilar density and air under both diaphragms.

Roentgenographic Examination

ROENTGENOLOGIST: First I want to show some films which were taken outside this institution. A chest film taken December 22 shows some nodular increase in the hilar densities; no findings. A gastrointestinal series made at that time demonstrates marked increase in the rugate pattern of the stomach and one can see evidence of pressure on the stomach, probably from a mass behind it. The mass most likely comprised enlarged lymph nodes, or possibly a retroperitoneal mass.

A chest film taken at Hines Hospital on January 4 shows an increase in the size of the hilar densities, indicating an increase in the hilar lymph nodes. There is also elevation of the diaphragm and evidence of pleural reaction at both bases (figure 1). This would go along with the presence of an epigastric mass and possibly some ascites.

Another gastrointestinal series made here at about the same time showed findings essen-

FIGURE 2. Lateral view of stomach and duodenum showing stomach displaced anteriorly. Note thickened rugae.

tially the same as before. The size of the gastric rugae and their irregularity were very marked. There was also a fuzzy irregular outline to the duodenal bulb. As far as I could tell fluoroscopically and from these films, there was no large ulceration of the stomach or the duodenal bulb. The possibility of small ulcerations cannot be ruled out on this examination, and certainly the possibility of involvement of the stomach wall by Hodgkin's disease or one of the lymphomas must be considered, although I do not think there is enough evidence for positive proof of this. The lateral film shows the stomach displaced anteriorly by a mass posterior to it (figure 2).

Films taken subsequent to the perforation show evidence of air and fluid levels in the abdomen, indicating that perforation had taken place and that there was fluid in the peritoneal cavity.

Diagnosis—Reticulum cell sarcoma, involving stomach, retroperitoneal and superficial lymph nodes; generalized peritonitis.

DR. VONDRASEK: The pertinent pathology included the following: The patient was slightly icteric, both the sclerae and the skin. There was a moderate amount of pitting edema over the lower extremities and extending up to the lumbar region, involving the scrotum. The abdomen was markedly distended. Nodes of the neck were mildly enlarged and there was a moderately enlarged right inguinal node.

On opening the chest, each pleural cavity contained about 460 cc. of amber-colored fluid. The right lung weighed 780 gm., and the left lung weighed 600 gm. Both lungs felt somewhat boggy in consistency. On cut section, they showed a grayish-red wet parenchyma. Microscopic examination revealed passive congestion.

On opening the peritoneal sac, a gush of foul-smelling air was noted; the sac contained about 4000 cc. of cloudy yellow-green fluid. All organs in the peritoneal sac were more or less covered with a thick, friable, greenish-yellow exudate. The small and large bowels were matted together with numerous adhesions.

The posterior wall of the stomach contained two clean-cut perforations about 2 to 3 cm. in diameter, and little or no inflammatory reaction was noted about these perforations (figure 3). There were large irregular areas that showed grayish-blue discoloration and erosion of the gastric mucosa. No inflammatory reaction was noted about these areas. The liver weighed 2,150 gm. and, on cut section, was a yellowish-red color; microscopically it showed central necrosis. The combined weight

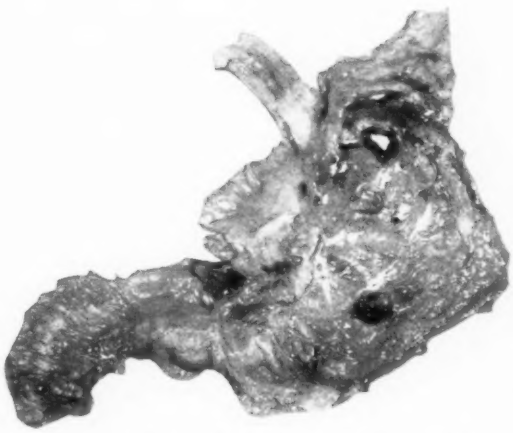

FIGURE 3. Opened stomach showing perforation near the esophagus and tumor infiltrates elsewhere in the wall.

of the kidneys was 420 gm., and they were pale and slightly edematous. The mesenteric, periaortic and mediastinal lymph nodes were all grossly enlarged and knotted together. Cut section showed a soft yellowish-red surface; microscopic section showed diffuse large areas of necrotic tumor. The tumor cell sections were unidentifiable. A thrombus, about 15 cm. long, was found in the left common iliac vein.

DR. COSTICH: Dr. Sophie Spitz of Memorial Hospital has summarized the changes in tissues in patients treated with nitrogen mustard. They show necrosis of all the tumor tissue and the typical balloon-type cells which are phagocytic. The spleen shows destruction of lymphoid follicles and marked congestion. The testicles show suppressed spermatogenic activity. Experimental work reported in the *American Journal of Pathology* showed that nitrogen mustard itself, in the absence of any tumor, will produce ulcerations in the intestinal tract. Of course, these studies all utilized lethal doses given to the animals, so whether or not this case would be comparable, I cannot say. This patient may have been more susceptible. It has been shown that nitrogen mustard injected into an animal will produce intestinal ulceration. This is a direct effect of the nitrogen mustard because it has also been shown, by tying off the vessels to a segment of the intestinal tract, that ingestion of nitrogen mustard produced ulcerations in the intestinal tract in all but the area which was tied off. So we may have a combination of circumstances in this case. In view of the fact that the patient did not have ulcerations in the remainder of the intestinal tract, it is likely that there was a direct action on tumor tissue which became necrotic and ulcerated away, leaving holes in the stomach wall.

DR. SLOBODIN: I can recall three patients who had perforations of the gastrointestinal tract following x-ray therapy so, even though resolution following x-ray is slower than with nitrogen mustard, there is no guarantee against perforation. This would be especially true with a condition like reticulum cell sarcoma rather than Hodgkin's disease. With Hodgkin's disease, when x-ray resolution occurs, there is replacement fibrosis, whereas with reticulum cell sarcoma, or small cell lymphosarcoma, no replacement by fibrosis occurs. That is, resolution occurs without fibrosis.

I think the choice of treatment in this case was proper because there was generalized involvement. With such generalized involvement x-ray therapy is protracted. While we are treating one area, another area may be increasing in size rapidly. Therefore, I think that in cases of generalized involvement, especially where the patient has constitutional symptoms, use of nitrogen mustard is indicated, followed very promptly—provided the blood count permits it—by x-ray therapy. In fact, I think that is the only indication for nitrogen mustard in treating any of the lymphomas. The literature usually states that nitrogen mustard is indicated when these lesions become radioresistant. I think the lesions do not become radioresistant. I think the patient becomes refractory to treatment because of generalized involvement, and if we treated one area of involvement during this so-called radioresistant phase, we would get as complete resolution as during early stages of the disease. The patient becomes refractory due to generalized involvement rather than an individual area becoming resistant to x-ray treatment. However, those patients who would die because of the rapid progression of the disease if they receive x-ray treatment, may recover sufficiently with nitrogen mustard therapy so that x-ray treatment can be given in the future with good results.

DR. COSTICH: In line with what Dr. Slobodin said, there are reports of "radioresistant" cases in which treatment with nitrogen mustard has produced very poor results.

Editorials

Postgraduate Medicine

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HISTOPLASMOSIS

ELSEWHERE in this issue there is an article* describing the clinical diagnosis of histoplasmosis. Since the evidence of the widespread character of this infection was first presented in 1945,[1,2] it has been of great interest to physicians, particularly in the Middle West. Epidemiologic studies have indicated that the disease is extremely prevalent in the Mississippi, Missouri and Ohio valleys—as many as 80 per cent of adults in these areas showing a positive skin test. The importance of this work has been difficult to evaluate because of a lack of knowledge of clinical characteristics of the illness caused by the fungus as well as the frequency of illness. Dr. Furcolow's paper is an attempt to outline at least a tentative category for the clinical diagnosis of this disease.

The classification of the clinical types of disease, if substantiated, would be extremely useful. For instance, in the so-called acute epidemic type where the pulmonary findings by x-ray are so striking, no fatalities were observed; whereas in the acute progressive type the course of the disease is short and the prognosis is usually bad.

The description of the so-called chronic progressive type is of great importance because of the finding that it is prevalent in tuberculosis sanatoriums. Since it is usually accompanied by pulmonary cavitation it is not surprising that such patients might be found in tuberculosis sanatoriums. However, finding 20 proved and over 100 probable cases of histoplasmosis in one sanatorium suggests that this problem is far more important than previously realized.

While this classification is labeled as preliminary, it should be very useful to physicians who are continually confronted with the problem of diagnosis of the patient in whom histoplasmosis is suspected.

Another problem is the absence of a satisfactory treatment. Treatment trials are under way, and it is obvious that this is a matter of extreme importance to the physician.

*FURCOLOW, MICHAEL L.: The clinical diagnosis of histoplasmosis, p. 349.

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2. CHRISTIE, AMOS and PETERSON, J. C.: Pulmonary calcification in negative reactors to tuberculin. Am. J. Pub. Health 35:1131-1147 (November) 1945.

BRITISH MEDICAL ASSOCIATION PRESIDENT GIVES HIS OPINION OF THE NATIONAL HEALTH SERVICE

At the annual session of the British Medical Association, held in Brighton during the first and second weeks of July, the address of its president, Dr. Alexander Hall, included a few sharp comments on the present status of the British National Health Service. Dr. Hall felt that the family doctor was likely to become far more important with the development of the scheme than he had been previously. Nevertheless, the general practitioner's service was suffering and he felt that it needs resuscitation if it is to survive. The process of disintegration has been progressive.

Dr. Hall is convinced that the government must give evidence of a change of policy if the family doctor's prestige is to be restored. These doctors want to be more than mere kingpins of a lifeless mechanical service. Dr. Hall, therefore, called on the British Medical Association and its members individually to preserve and foster the practice of medicine outside the national service "away from the cold blast of bureaucratic control. The greater the area of freedom provided by the private practice of medicine," Dr. Hall continued, "the greater would be the encouragement to maintain a general high standard. The doctor must be his own master and able to mold his practice according to his own temperament and capacity." He did not have any definite advice as to how these effects could be brought about. He did say, however, "Somehow or other the Association must bend its efforts for not only preserving but also enlarging the area of freedom and dignity in medicine that still exists within the framework of the National Health Service." He continued, "If we cannot succeed in this, then I fear for the future of medicine and especially of general practice."

These statements by the distinguished president of the British Medical Association again confirm the numerous fears expressed by physicians during the time when the National Health Act was being formulated. An old proverb refers to chickens that come home to roost. Apparently a great many chickens of this type have been hatched out in the medical practice that has prevailed in Britain in the years since the National Health Act first became effective.

MORRIS FISHBEIN

IRRADIATION OF THE THYROID AND CANCER

Stimulated by suggestions in various medical publications that irradiation might be a causative factor in cancer of the thyroid in children and adolescents, Dr. Dwight E. Clark[1] made a search of the literature to ascertain whether anyone had previously correlated such treatments with a subsequent development of cancer of the thyroid. He could not, however, find any such references. Apparently, the possibility that this might occur was suggested by Duffy and Fitzgerald, who found that 10 of 28 cases seen in Memorial Hospital, New York, had been subjected to irradiation of the thymus gland sometime between the fourth and sixteenth months of life. Simpson and others studied the incidence of cancer in 1400 children who had had irradiation of the thymus and they found the number of cases of cancer of the thyroid significantly higher in this group than in their brothers and sisters who had not been irradiated, or in the general population.

Dr. Clark, therefore, decided to investigate the record of previous irradiation in cases of cancer of the thyroid in children under 15 years of age. Thirteen cases were studied: Three had had irradiation of the upper chest for enlarged thymus; three irradiation of the neck for cervical adenitis; five irradiation for enlarged tonsils; one irradiation for peribronchitis, and one for persistent pertussis. Through correspondence with other surgeons, two other cases were found in which one patient had been irradiated for thymic enlargement and the other for chronic cough. The patients studied had ranged in age from two months to six years at the time of irradiation; their ages at the time of histologic diagnosis of cancer varied from 4 to 15 years.

Dr. Clark points out that cancer of the thy-

roid in children and adolescents is still relatively uncommon, but the number of cases diagnosed is increasing. The increase corresponds to the period when irradiation was being widely used for benign conditions of the head, neck and thorax. While the evidence is small in amount and obviously statistical, the observations support the concept that there may be an association between prior irradiation and cancer of the thyroid in children and adolescents.

MORRIS FISHBEIN

REFERENCE

1. Clark, Dwight E.: Report to Chicago Surgical Society meeting, May 6, 1955. Proc. Inst. Med. Chicago (May) 1956.

SCIENCE AND CONSISTENCY

The British Medical Association met on July 5 at Brighton for its 124th annual representative meeting. In its report of the meeting the *London Times* says:

"Although a majority of the doctors (173 to 154) were in favour of smoking during the meeting, the necessary majority of three-quarters was not obtained, and a standing order prohibiting smoking during proceedings, which is usually quickly disposed of, could not be suspended on this occasion."

The account of the meeting indicates that there was much heat but little light in the course of the discussion.

At the same session of the British Medical Association's representative body a resolution protesting the ban by the Government of the right to prescribe heroin was approved. The resolution reads:

"Following the recent attempt by the Government to ban the prescription of heroin, this meeting affirms as a matter of principle its determination to preserve the right of any individual doctor to prescribe what he thinks is in the interests of his patient."

This distinction between individual liberties will no doubt provoke the risibilities of those who love to cast barbs of satire on what is commonly called "the scientific mind."

At one of the earliest meetings of the American Medical Association in the 1840s a resolution introduced by Dr. N. S. Davis, the founder, who was an ardent teetotalitarian, forbade the serving of alcoholic liquors at any official functions of the Association. The number of cocktail parties before official functions is rising steadily and the hotels have not reported any sharp decrease in the amount of alcoholic liquors served during meetings of the Association. On the contrary!

MORRIS FISHBEIN

CONTROL OF DENTAL CARIES BY FLUORIDATION

Grand Rapids, Michigan, Newburgh, New York, and Brantford, Ontario, have been adding fluoride to their water supplies for 10 years. In 1945 systematic examinations were made of the teeth of considerable numbers of children 6 to 10 years of age in each of these communities. Re-examinations were made each year. The reductions in dental caries in each city for each age group were remarkably similar, although the studies were made completely independently. They approximate, moreover, the rates previously recorded for Aurora, Illinois, where the public water supply contains naturally 1.2 parts per million of fluoride. These figures, cited by H. Trendley Dean[1] and supported by vast amounts of similar evidence from all over the world, make one wonder at the resistance that has developed to this new step in preventive medicine.

By the end of 1955 about 1100 communities in the United States with a total population of over 20 million were using fluoridated water supplies. Among the cities which now utilize this measure are Milwaukee, Indianapolis, Philadelphia, Baltimore and Miami. Denver has an optimal amount of fluoride in its natural water supply.

The campaign against fluoridation has attracted all the fringe elements that align themselves against animal experimentation and inoculation against infectious diseases, some even against blood transfusion. Unfortunately even a few physicians and scientists seem to be completely unwilling to be convinced of the safety and benefits of fluoridation by the

mass of evidence now assembled in its behalf. Dr. Charles Richet said that *Homo sapiens* ought to be called *Homo stultissimus* because he so often fails to avail himself of what scientific knowledge provides to relieve him of pain and disease.

MORRIS FISHBEIN

REFERENCE

1. Dean, H. T.: The control of dental caries by fluoridation. Report of meeting of the Odontographic Society of Chicago, October 3, 1955. In: Proc. Inst. Med. Chicago (May) 1956.

MULTIPLYING ADMINISTRATIVE PERSONNEL

One of the most significant developments in connection with governmentally controlled medical institutions is the rate of multiplication of administrative personnel. In some countries this number has increased to tremendous heights and represents the greatest cost of providing medical service. In most instances there are certainly as many as two administrators for every physician in the service.

Now from Great Britain comes information indicating that the tremendous increase of persons involved in hospital administration is giving great concern to both the government and the medical profession. According to a statement by Dr. Claudius F. Mayer,[1] the small hospitals were formerly administered by a house governor, a clerk and a lay committee; now the staff of such institutions has been multiplied many times. The increase is due to the tremendous number of forms that must be filled out, the payment of salaries to honorary staff members, the formation of a new crop of committees, and the number of reports that must be made to higher authorities. Here again, as mentioned in a previous editorial on this subject in Postgraduate Medicine, is coming to factual existence a prediction that was made in 1937 when the United States government began most seriously to threaten taking over medical service.

More serious, however, than the growth of administrative personnel and the cost is the change in doctor-patient relationship that is taking place. The excessive number of patients coming to doctors' offices and hospital wards, in many instances without any actual need, is leading to failure in making scientific diagnosis and to application of more and more symptomatic treatment based on a simple relation of the patient's complaints. Moreover, young physicians are being drafted into grooves from which they cannot move without reverting to the lowest grade of appointment and beginning again in a new channel should they wish to change the direction of their medical service.

MORRIS FISHBEIN

REFERENCE

1. Mayer, Claudius F.: Around the world. Mil. Med., April 1956.

COXSACKIE VIRUS AND MYOCARDITIS

At the Third International Poliomyelitis Conference in Rome, September 1954, J. H. S. Gear discussed various epidemics of myocarditis caused by the Coxsackie virus. Now Dr. S. Van Creveld and Dr. H. DeJager[1] have described four such cases in newborns which occurred in 1955 during an epidemic of "summer grippe" in adults in Amsterdam. Laboratory studies proved the presence of the Coxsackie virus as the etiologic agent. In each instance the mothers had symptoms of influenza. At necropsy the myocarditis was found and demonstrated histologically. Foci of infection also were found in the liver and brain. The lesions of the heart were, however, similar in all the cases. In most cases the onset is sudden, beginning with dyspnea, paleness, cyanosis often with spasmodic coughing, and sometimes tachycardia. Soon symptoms of cardiac decompensation with enlargement of the heart and liver appear. The electrocardiogram, according to Van Creveld, always shows signs of severe damage to the myocardium.

Since 1948, when the Coxsackie viruses were first called to medical attention by Dalldorf and Sickles, they have been considered important chiefly in relationship to the condition called epidemic myalgia or pleurodynia.

The Coxsackie viruses are widely distributed and are believed to be responsible chiefly for these and other self-limited conditions. Indeed, Joseph L. Melnick and Edward C. Curnen[2] stated that distinctive lesions have not been observed in patients infected by Coxsackie viruses, and that information is lacking concerning the histopathologic picture in man of infection with these viruses because deaths attributable to them have not been reported. The report by Van Creveld, meticulously developed and complete with studies of the virus and of the pathology, makes clear the possibility that in cases such as those of the young infants described the Coxsackie virus may produce death through attack on vital tissues.

MORRIS FISHBEIN

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2. Melnick, J. L. and Curnen, E. C.: The Coxsackie group. In Rivers, T. M.: Viral and Rickettsial Infections of Man. Ed. 2. Philadelphia, J. B. Lippincott Company, 1952.

TOTAL REHABILITATION

Dr. Howard A. Rusk has said, "Webster's definition of rehabilitation is 'returning one to his former state.' This is rather a sad objective when you are dealing with congenital deformity. So I prefer another definition. It goes like this: 'Rehabilitation is a total program designed to meet the total needs of the handicapped person so that he may lead the best possible life to the hilt of his ability, and in dignity.' "

In 1889 the Association for the Care of Cripples was established in Finland, and in 1890 a small school for cripples was begun in Helsinki. Only seven pupils were included in the first course, but the number increased rapidly. Success of these early courses led to the completion in 1897 of an institution with 50 pupils in spacious classrooms and workshops. In 1900 an outpatient department was opened and in 1927 an orthopedic hospital was built adjacent to the school. During the war with Russia an Invalid Foundation was established for the care of ex-servicemen and to provide for total rehabilitation of the crippled.

In June 1940 the previous efforts of Finland were united under the leadership of the Ministry for Social Affairs which joined with the Society for Assistance to the Cripples, the People's Pensions Board, the Association of Finnish Civilian and Conscript Invalids, and the Association of Accident Insurance Establishments to found the Invalid Foundation which aims at total rehabilitation of cripples. The various buildings of this organization in Helsinki, with branches in other parts of Finland, now constitute one of the greatest rehabilitation centers in the world. Among the buildings are an orthopedic hospital with 150 beds, an outpatient department, a vocational school with such departments as metals, woodworking, radio service, upholstering, tailoring, shoemaking, domestic science, millinery and dressmaking, a department for vocational guidance with psychologists and a testing laboratory, an orthopedic shoeshop, a gymnastic institute, and a prosthetic shop. There is also a nurses' home as well as an inn in which patients from a distance may remain while their cases are being studied for assignment.

The spirit of these institutions resembles what one observes at the Georgia Warm Springs Foundation and in the Institute for Rehabilitation associated with Bellevue Hospital. The handicapped persons are hopeful, optimistic, and determined to make the most of themselves. This concept of total rehabilitation arose from the leadership of Professor F. Langenskiöld who has guided the work since its earliest days and who will retire this year because of age. His inspiration and devotion have lightened the lives of thousands of cripples all over the world.

MORRIS FISHBEIN

THE EVOLUTION OF INFANT FEEDING

In the Windermere Lecture, given by Dr. Alton Goldbloom[1] before the British Paediatric Association in 1954, he praised the way in which our views of infant feeding have changed during the last 75 years. From a time

when the chief question in infant feeding was the amount to be put into the infantile stomach, through a period when pediatricians tried to feed infants with preparations of fundamental food materials calculated in fractions of percentages, to the present when a more rational view begins again to prevail, the story is a fascinating portrayal of the evolution of medical science.

One remembers the period of wet-nursing, the collection of human milk for storage, the search for a satisfactory substitute for human milk, and then, in 1905, the first studies of the chemical composition of human milk and a comparison with cow's milk. Since that date more and more attempts are being made to simulate human milk, regulating the content of lactalbumin, casein and salts. Homogenization was introduced to break up the fat droplets. With this came the introduction of SMA®, SIMILAC® and other formulas. For a while sugars gave chief concern to the pediatricians, and the center of pediatric attention varied from lactose to honey to sucrose, malt sugar and other preparations. Dr. Goldbloom's story carries the reader through the period of acidified milk *(Eiweissmilch)*, simple boiling of milk, and to the more recent emphasis on vitamins and enzymes. In the midst of all this physicians recognized, of course, the necessity to keep milk clean and later to make sure that it was free from germs; then came the great epoch of certified milk with medical committees and schemes for distribution.

Today, infant feeding has been simplified. The three principles that prevail demand adequacy of the product, sterility, and inclusion of essential vitamins and minerals. Summarizing, Dr. Goldbloom states the requirements: . . . "the provision of an amount of whole milk sufficient to meet the fat and protein requirements of the infant, and the addition of sufficient sugar, any sugar, to supplement the caloric deficiency of the milk allowance with sufficient water to meet the fluid needs of the infant and the provision of adequate vitamin supplements."

MORRIS FISHBEIN

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1. Goldbloom, A.: The evolution of the concepts of infant feeding. Arch. Dis. Childhood 29:385-390 (October) 1954.

OCCUPATIONAL HEALTH

In Finland an Occupational Medical Foundation sponsors an Institute of Occupational Health under the direction of Dr. Leo Noro. The Occupational Medical Foundation was organized in 1945 by representatives of industry, insurance and medicine. On the board of the Foundation are representatives of most important governmental bodies, the state medical board, the ministers of social affairs, interior affairs, communications, and public works; the medical faculty of Helsinki University, the Finnish Institute of Technology, and various insurance agencies. Also represented are the Central Federation of Employers, the Federation of Finnish Trade Unions, and the city of Helsinki.

Before the Institute was constructed, Dr. Leo Noro, on a scholarship from the Rockefeller Foundation, visited a number of foreign countries to study similar projects. Built under an act of Parliament, the Institute functions with a staff of 143 persons. It has a statistical section, a counseling section for disabled persons, and a medical department which provides treatment for those with occupational diseases or conditions suspected of being connected with their work. Workers are examined to assess their working capacity, and mass investigations are made to detect tuberculosis, and to check sight, hearing and environmental hygiene.

In the research section investigations have been made of the strain imposed by various jobs and the energy used in their performance, the effects on the human body of different types of work, cardiac function in relation to working capacity, muscular strength and endurance, the toxic effects of substances used in industry, and physical fitness in relation to sports. The psychologic division has made aptitude tests and studied vocational training, job placement, prevention of accidents, fatigue, and human relations.

Here again is an example of cooperation among government, industry, private philanthropy and individuals in meeting a health need that is often greatly neglected.

MORRIS FISHBEIN